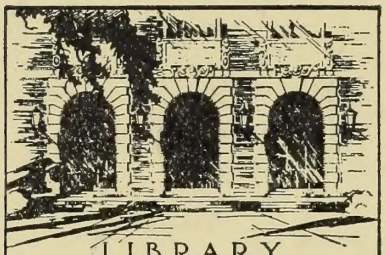


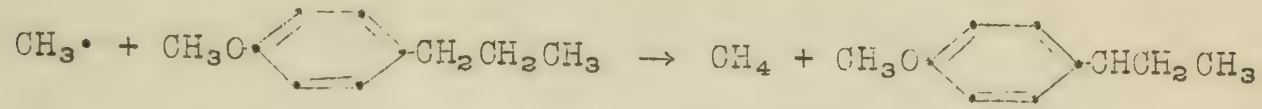
SEMINAR TOPICS

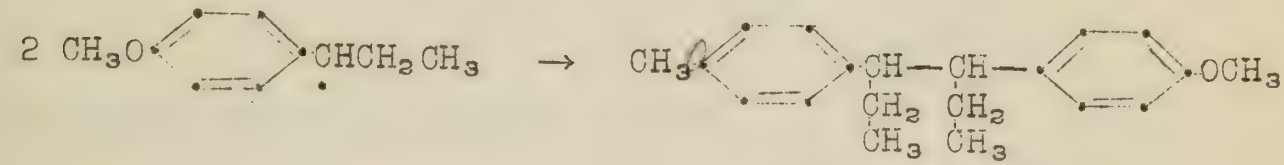
I Semester 1947-48

PREPARATIVE REACTIONS INVOLVING FREE RADICALS

Bibenzyls (26)

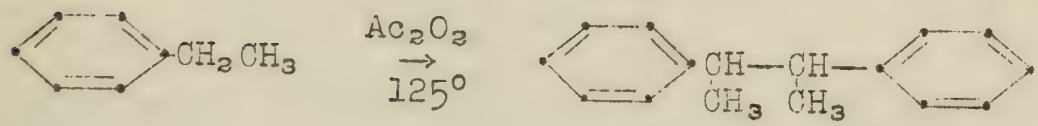
(1) $CH_3CO{\cdot}O{\cdot}O{\cdot}COCH_3 \xrightarrow{125^\circ} CH_3{\cdot} + CO_2 + CH_3COO{\cdot}$





91% (meso and racemic)
Hexestrol Dimethyl Ether

(2)



92% (meso and racemic)

(3)

95%

Halogenated Hydrocarbons (27,28)

$CH_3(CH_2)_5CH{=}CH_2 + CCl_4 \xrightarrow[\text{or } Bz_2O_2]{Ac_2O_2} CH_3(CH_2)_5CH(Cl)CH_2CCl_3$

$CH_3(CH_2)_5CH{=}CH_2 + CHCl_3 \rightarrow CH_3(CH_2)_5CH_2CH_2CCl_3$

$CH_3(CH_2)_5CH{=}CH_2 + CHBr_3 \rightarrow CH_3(CH_2)_5CH(Br)CH_2CHBr_2$

$CH_3(CH_2)_5CH{=}CH_2 + CHBrCl_2 \rightarrow CH_3(CH_2)_5CH(Br)CH_2CHCl_2$

$CH_3(CH_2)_5CH{=}CH_2 + CBr_4 \xrightarrow{u.v.} C_6H_{13}CH(Br)CH_2CBr_3$ (88%)

$C_2H_5 + CBr_4 \xrightarrow{u.v.} CH_2BrCH_2CBr_3$

$\emptyset CH{=}CH_2 + CBr_4 \xrightarrow{u.v.} \emptyset CH(Br)CH_2CBr_3$ (100%)

$\emptyset CH{=}CH_2 + CCl_4 \xrightarrow{u.v.}$ Polymers

$\emptyset CH{=}CH_2 + CBrCl_3 \xrightarrow{u.v.} \emptyset CH(Br)CH_2CCl_3$ (no polymers)

Halogenated Acids (29)

$$\text{1-Octene} + Cl_2CHCOOCH_3 \xrightarrow[100^\circ]{Ac_2O_2} C_8H_{17}CCl_2COOCH_3$$

$$\text{1-Octene} + Cl_3CCOCl \rightarrow C_6H_{13}\underset{Cl}{CH}-CH_2-CCl_2COCl$$

(81%)

Dicarboxylic Acids and Esters (30,31)

$$ClCH_2COOH \xrightarrow{Ac_2O_2} HOOC\underset{Cl}{CH}-\underset{Cl}{CH}COOH$$

(meso and racemic)

$$ClCH_2COOCH_3 \xrightarrow{Ac_2O_2} \overset{H}{Cl}\underset{COOCH_3}{C}-\overset{Cl}{\underset{COOCH_3}{C}}-\overset{H}{\underset{COOCH_3}{C}}Cl + \overset{H}{Cl}\underset{COOCH_3}{C}-\overset{H}{\underset{COOCH_3}{C}}Cl$$

(27%) (60%)

$$FCH_2COOCH_3 \xrightarrow{Ac_2O_2} CH_3OOC\underset{F}{CH}-\underset{F}{CH}COOCH_3$$

(53%)

$$CH_3COCH_2COOCH_3 \xrightarrow{Ac_2O_2} CH_3CO\underset{COOCH_3}{CH}-\underset{COOCH_3}{CH}COOCH_3$$

$$\begin{matrix} CH_2-COOCH_3 \\ CH_2-COOCH_3 \end{matrix} \xrightarrow{Ac_2O_2} \begin{matrix} CH_2COOCH_3 \\ CHCOOCH_3 \\ CHCOOCH_3 \\ CH_2COOCH_3 \end{matrix}$$ (meso and racemic)

$$\emptyset CH_2COOCH_3 \xrightarrow{Ac_2O_2} \begin{matrix} \emptyset CHCOOCH_3 \\ \emptyset CHCOOCH_3 \end{matrix}$$ (meso and racemic)

Aldehydes and Ketones (32)

$$CH_3(CH_2)_2CHO + \text{1-hexene} \xrightarrow{Ac_2O_2} CH_3(CH_2)_2\overset{O}{\overset{\|}{C}}(CH_2)_5CH_3$$

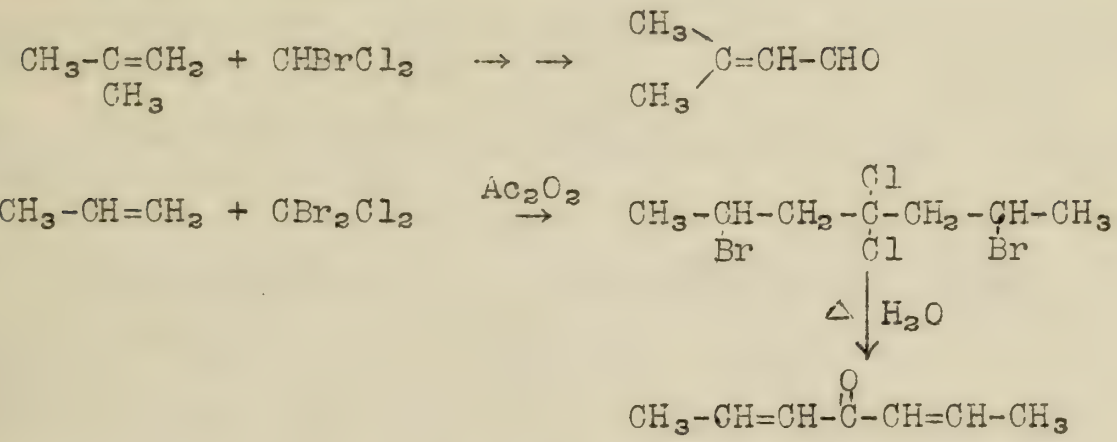
$$CH_3(CH_2)_5CHO + \text{1-octene} \rightarrow CH_3(CH_2)_5\overset{O}{\overset{\|}{C}}(CH_2)_7CH_3$$

$$CH_3(CH_2)_5CH{=}CH_2 + CHBrCl_2 \xrightarrow[70^\circ\ 6\text{ hrs.}]{Ac_2O_2} CH_3(CH_2)_5\underset{Br}{CH}-CH_2CHCl_2$$

$$\downarrow \Delta, H_2O$$

$$CH_3(CH_2)_5CH{=}CH-CHO$$

Aldehydes and Ketones (cont'd.)



Compounds Containing Si or P (33,34)

1-Octene + PCl_3	$\xrightarrow[Ac_2O_2]{(N_2)\ 85^\circ}$		$C_8H_{16}Cl\text{-}PCl_2$
1-Octene + $SiHCl_3$	$\xrightarrow[Ac_2O_2]{(N_2)\ 45^\circ}$	99%	$C_8H_{17}SiCl_3$
	$\xrightarrow{u.v.}$	24%	$C_8H_{17}SiCl_3$

Reported by Nelson J. Leonard
October 10, 1947

FREE RADICAL REACTIONS

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For halogenated hydrocarbons:

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31. Kharasch, McBay, and Urry, J. Org. Chem., 10, 394 (1945).

For aldehydes and ketones:

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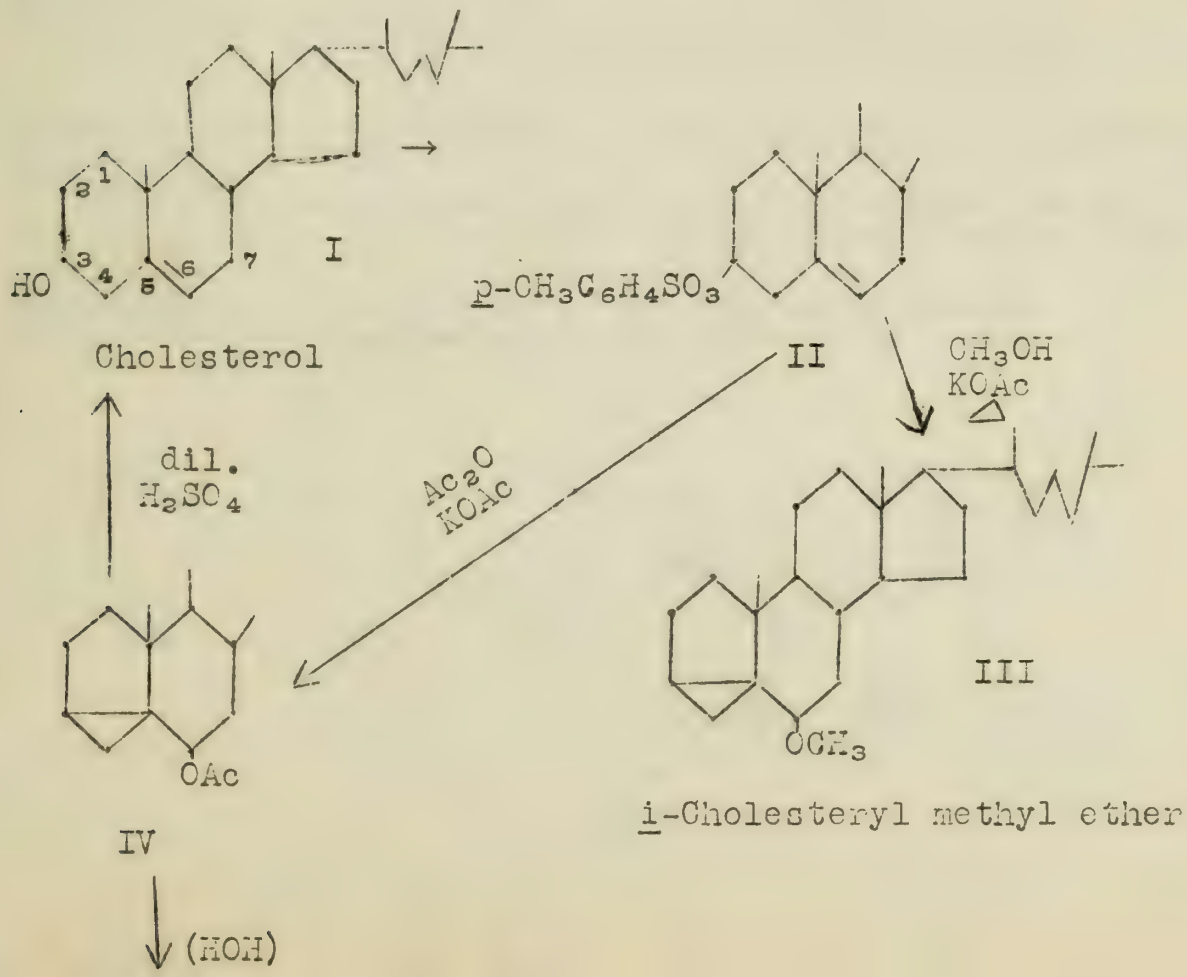
Nelson J. Leonard
October 10, 1947

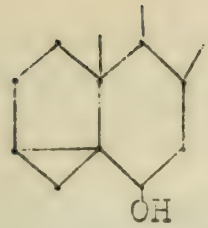
i-STEROIDS

Introduction.--i-Steroids are sterol derivatives of which Structure III is an example. They were first prepared in 1932 by Stoll (1,2,3) during an investigation of the formation of cholesteryl ethers from the p-toluenesulfonyl (tosyl) ester of cholesterol (II). If this ester is refluxed with methanol (or other alcohols), the normal ether of cholesterol is formed. If anhydrous potassium acetate is added, however, an isomeric ether is formed. Stoll and others (4) considered this isomer to be a C_3 epimer of the normal cholesteryl ether.

Beynon, Heilbron and Spring (5,6,7), in a search for methods of preparing epi-cholesterol, studied the formation and properties of this isomeric methyl cholesteryl ether. In spite of its lack of stability when compared with normal cholesteryl ethers, and the abnormally high dextrorotation when compared with similar compounds (8), these authors considered the chief difference in the isomers to be in the configuration at C_3.

Sturcture of i-Steroids.--The true nature of the isomeric cholesteryl ether mentioned above has been demonstrated by Wallis and his group at Princeton in a noteworthy series of papers beginning in 1937 (9,10,11,12). The structure is that represented by Structure III and the name i-steroid has been proposed by Wallis for such compounds.





V

During the course of the structure elucidation it was shown that the isomerization is not confined to ethers. For example, treatment of the p-toluenesulfonyl ester (II) with acetic anhydride and potassium acetate gives i-cholesteryl acetate (IV). This can be hydrolyzed under mild conditions to i-cholesterol istelf (V). Acid conditions reconvert the i-derivatives to normal cholesteryl derivatives.

The isomerization is general for sterols with hydroxyl groups at C_3 and unsaturation at C_5-C_6.

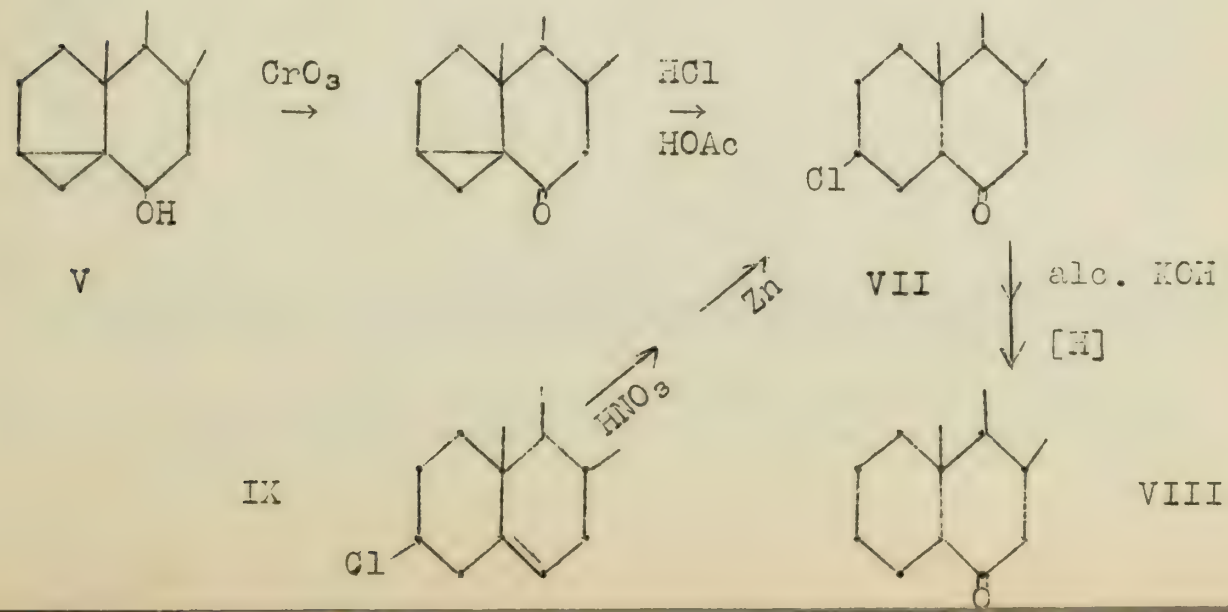
The essential facts in the structure proof are as follows:

Evidence that C_5-C_6 double bond has disappeared:
Catalytic hydrogenation occurs only with difficulty.
No reaction with perbenzoic acid.
No decolorization of bromine in carbon tetrachloride.

Evidence that i-cholesterol is a secondary alcohol:
It can be oxidized to a ketone (VI) (isolated as its oxime).

Evidence that i-cholesteryl methyl ether is not C_3-epi-cholesteryl methyl ether:
The C_3 epimeric ether was prepared by another method (10,13) and shown to be different from i-cholesteryl methyl ether.

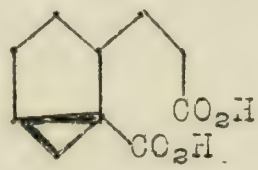
Degradation of i-cholesterol to a known C_6 ketone:



Cholestanone-6 (VIII) had been previously prepared by Windaus and Dalmer (14) by Steps IX-VII-VIII and was identical with the compound obtained by Ford, Chakravorty and Wallis (11). Thus the hydroxyl group in i-cholesterol is on C_6.

Further chemical evidence:

i-Cholestanone (VI) has been oxidized by means of potassium hypobromite to a dicarboxylic acid (12) thought to be Structure X.



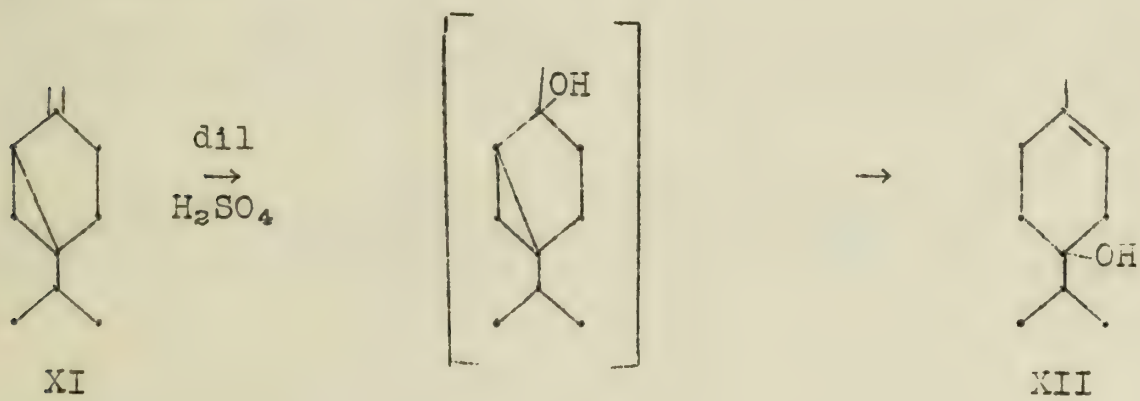
X

Physical evidence:

Ultraviolet spectra of some of the i-steroids corroborate the pentacyclic structure (III,IV,V) (15).

At the completion of Wallis' work, the English workers in the field, Beynon, Heilbron, Hodges and Spring (5,6,7,16) acknowledged its correctness in all but a few details.

It was subsequently pointed out (12) that this type of isomerism is not entirely new, but had been observed (in reverse) by Wallach (17) and others (18) in studies in the thujane series of terpenes:



XI

Sabinene

XII

Properties and Reactions of i-Steroid Derivatives.--Present knowledge may readily be summarized in the following lines:

The i-structure resists mild hydrogenation; stronger conditions yield reduced products of the normal steroid isomers

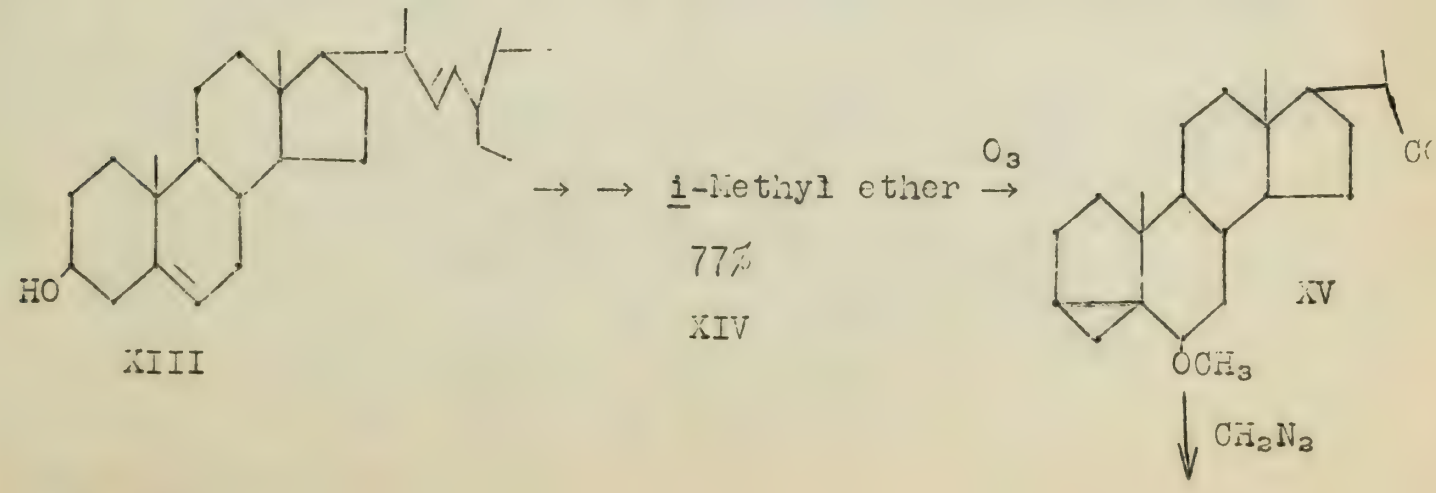
(1,6,9,19). i-Ethers are converted by alcoholic mineral acids (usually sulfuric) to normal ethers (3,20). i-Ethers are converted by halogen acids in glacial acetic acid or by acyl halides in pyridine to the normal steryl halides (cholesteryl iodide was prepared for the first time by this means) (5,6,19). i-Ethers react slowly with bromine to give 3,5,6-tribromo derivatives (5,6,19). i-Ethers or i-acetates are converted to normal acetates by heating with glacial acetic acid; they are converted to normal hydroxyl derivatives by means of aqueous acids (9,19).

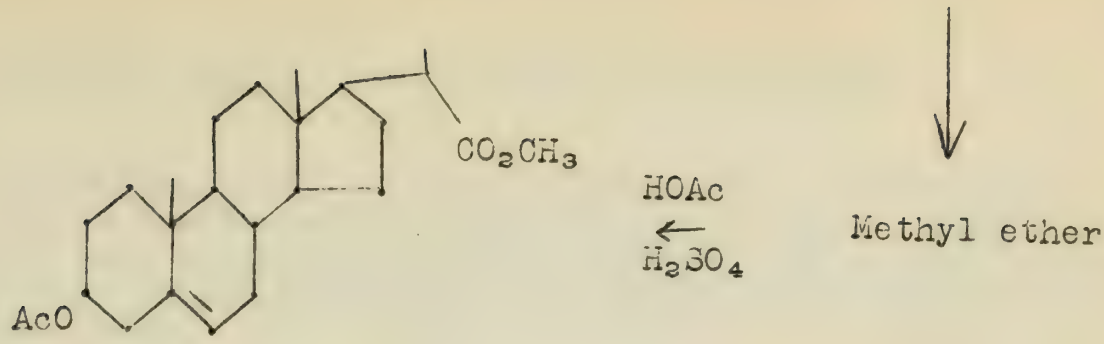
The i-structure can be converted to the normal structure without hydrolysis of semicarbazone groupings in other parts of the molecule (21).

Catalytic hydrogenation of double bonds is successful in other parts of the molecule without disturbing the i-structure (22). i-Structures are resistant to perbenzoic acid and mild permanganate and chromic acid oxidation (9,16,23). The i-structure is not attacked by the Grignard reagent (24). It is generally rearranged under the conditions necessary to dehydrate carbinol groupings in other parts of the molecule (this causes difficulties if the Barbier-Wieland degradation is tried on i-steroids) (24,25). The i-structure withstands the use of ozone to oxidize other parts of the molecule (21,26).

Synthetic Applications of i-Steroid Isomerizations.--As suggested by the preceding section, formation of the i-structure in certain sterols can be used to protect the 3-hydroxy-5,6-double bond while variations are made in other parts of the steroid nucleus. Work thus far, notably by Riegel and coworkers (19,24, 25,26,27), indicates much promise for the method, especially since two of the cheapest and most readily available sterols, cholesterol and stigmasterol, have the 3-hydroxy-5,6-unsaturated structure, and the sex hormones progesterone, testosterone and androsterone have related or derived structures in the A and B rings.

An example is the conversion of stigmasterol (XIII) to methyl 3-acetoxy-5-bisnor-cholenate (XVI), a promising intermediate in some proposed syntheses of naturally-occurring hormones (26):





XVI

The method is superior to the well-known protection of the hydroxyl group and double bond by formation of the dibromo acetate before ozonolysis. The yields are high (ca. 80%).

Among others (19-21,23-25,27,28), a useful application of Fernholz and Ruigh (22) concerns the reduction of the side chain double bond in stigmasterol (XIII) without reduction of the 5,6-double bond.

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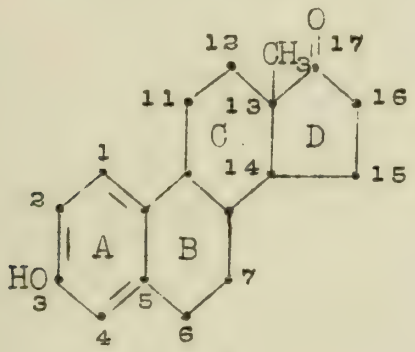
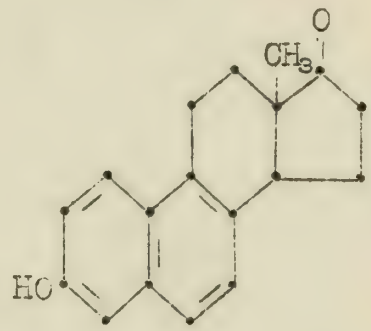
Reported by Robert L. Frank
October 17, 1947.

COMPOUNDS RELATED TO THE FEMALE SEX HORMONES

In 1939, Bachmann and colleagues[1] completed a successful synthesis of the female sex hormone Equilenin. Since that time a program has been in progress on the synthesis of compounds similar in structure to the naturally occurring hormones Estrone (I) and Equilenin (II).[2]



I

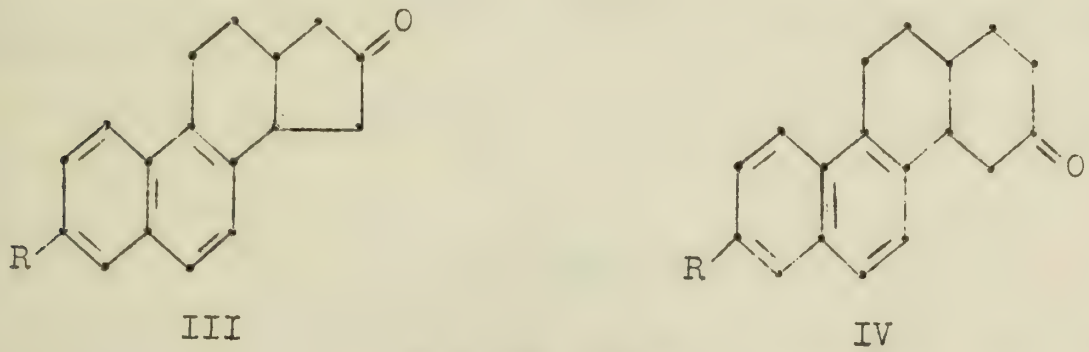


II

To date, the following analogs have been prepared:

(1) Rings "A" and "B" absent.[2l]
(2) Ring "A" absent; "B" unsaturated.[2d]
(3) Same as (2) but with an -OH group in position corresponding to 5 above.[2e]
(4) Hydroxyl group in position 3 absent; ring "B" unsaturated.[2a]
(5) Hydroxyl group in position 6 rather than 3; ring "B" unsaturated.[2b]
(6) Same as (5) but an ethyl group rather than a methyl in position 13.[2b]
(7) Same as (5) but the "D" ring is expanded to six carbon atoms.[2b]
(8) Same as II but an ethyl group rather than a methyl in position 13.[2c]
(9) Same as II but an n-propyl group rather than a methyl in position 13.[2k]
(10) Same as II but an n-butyl group rather than a methyl in position 13.[2k]
(11) Same as II but an additional methyl group in position 16.[2k]
(12) Same as II but the "D" ring is expanded to six carbon atoms.[2k]
(13) Hydroxyl group in position 6 rather than 3; "A" ring saturated.[2f]
(14) Hydroxyl group in position 2 rather than 3.[2j]
(15) Hydroxyl group in position 1 rather than 3.[2l]
(16) Diastereoisomers of Estrone I.[2g]
(17) Same as II but methyl group in position 13 absent.[2h]
(18) Same as II but methyl group in position 13 absent; "D" ring is expanded to six carbon atoms.[2h]
(19) Same as II but hydroxyl group in position 3 is absent; "A" ring is saturated.[2i]

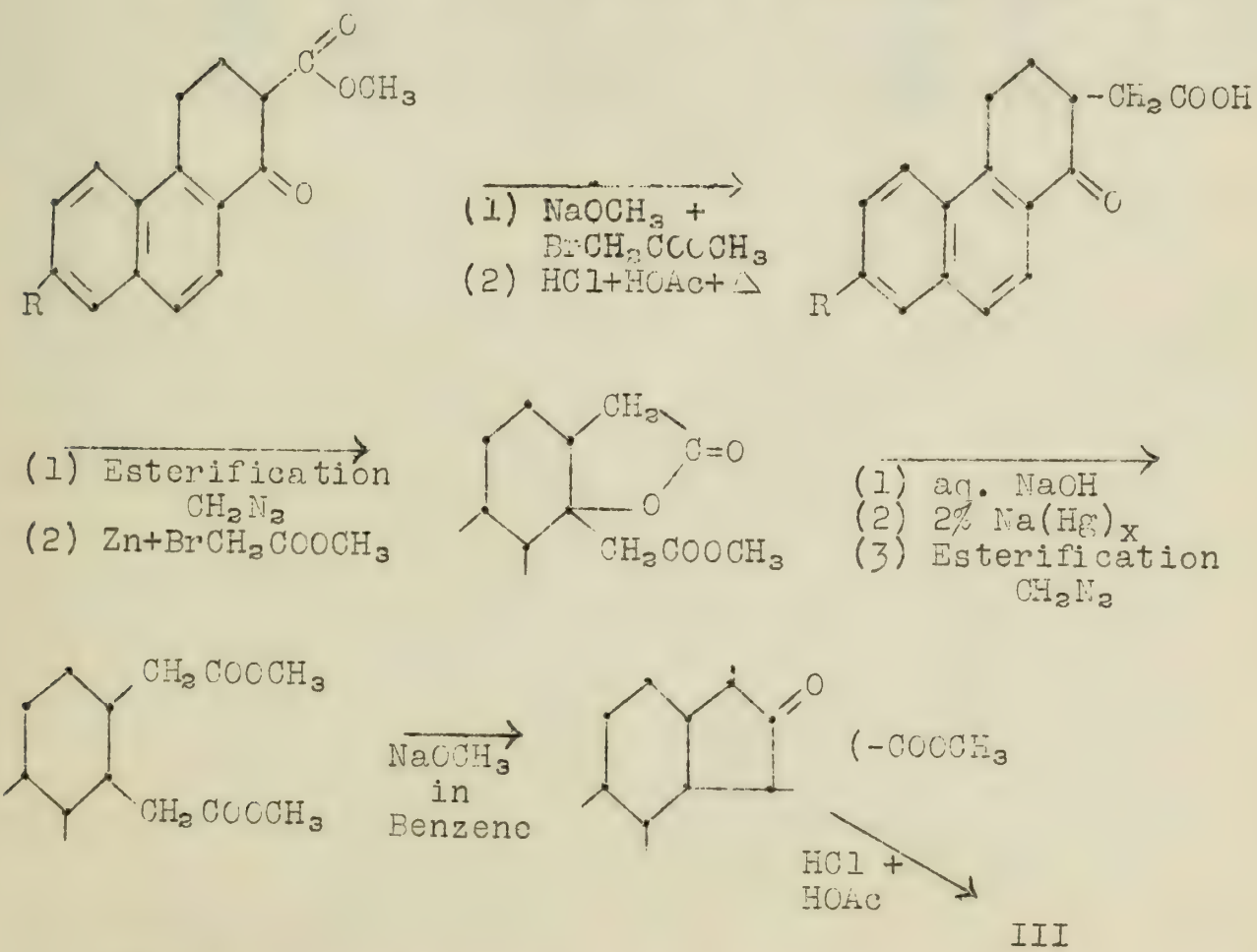
The new compounds (III, IV)[2m] reported today are a part of the program as outlined above. These compounds lack the angular methyl group found in Equilenin and in addition the carbonyl group is displaced from position 17 to position 16. In two of the compounds the "D" ring is enlarged to six carbon atoms with consequent position shift of the carbonyl group.



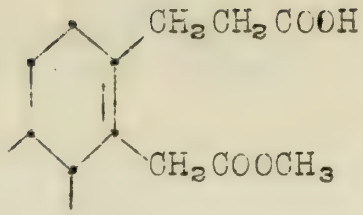
III IV

R = -H, -OH

The syntheses of III proceeded according to scheme:



The syntheses of compounds IV were similar to III with the exception that methyl beta-bromopropionate or acrylonitrile were used rather than methyl bromoacetate. In addition, the Reformatzky product proved to be the unsaturated acid:



which required more drastic treatment with sodium amalgam before being reduced.

None of these analogs were more active than Estrone.

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(2) Bachmann and coworkers:
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(b) ibid., 62, 2750 (1940);
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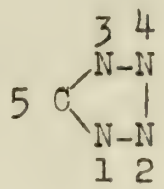
(d) ibid., 63, 598 (1941);
(e) ibid., 63, 94 (1941);
(f) ibid., 64, 536 (1942);
(g) ibid., 64, 974 (1942);
(h) ibid., 65, 2314 (1943);
(i) ibid., 66, 553 (1944);
(j) ibid., 69, 58 (1947);
(k) ibid., 63, 2592 (1941);
(l) Unpublished work;
(m) In press.

Reported by L. E. Miller
October 17, 1947

THE CHEMISTRY OF THE TETRAZOLES

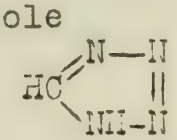
The tetrazoles are doubly unsaturated five membered ring heterocyclics containing one carbon and four nitrogen atoms. The simplest and preferred nomenclature numbers the ring atoms in the order:



The first tetrazole was synthesized by J. A. Bladin in 1885 by the action of nitrous acid on dicyanophenylhydrazine yielding 5-cyano-1-phenyltetrazole.[1] From this derivative tetrazole itself was prepared several years later.

Syntheses.--The two principal methods employed in the synthesis of the tetrazoles are (1) the action of hydrazoic acid or an azide on a cyano, isocyano, imido or carbonyl group and (2) the action of nitrous acid on a hydrazine derivative. The following are general and illustrative preparations:

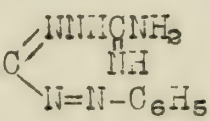
T = tetrazole

1. $HCN + HN_3 \xrightarrow[\text{alcohol}]{\text{dry}}$  (2)

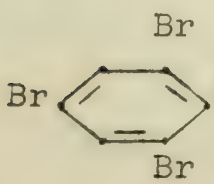
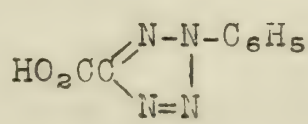
2. $NH_2CN + HN_3 \rightarrow 5\text{-}NH_2T$ (3)

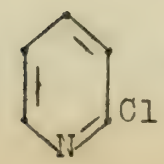
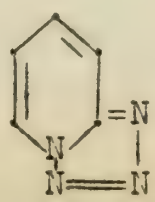
3. $C_6H_5NC + HN_3 \rightarrow 1\text{-}C_6H_5T$ (4)

4. $p\text{-}CH_3C_6H_4C(=NH)NHNH_2 + HNO_2 \rightarrow 5\text{-}CH_3C_6H_4T$ (5,6)

5. $C_6H_5CH{=}NNHC(=NH)NH_2 + C_6H_5N_2Cl \rightarrow$  $\xrightarrow{HNO_2}$

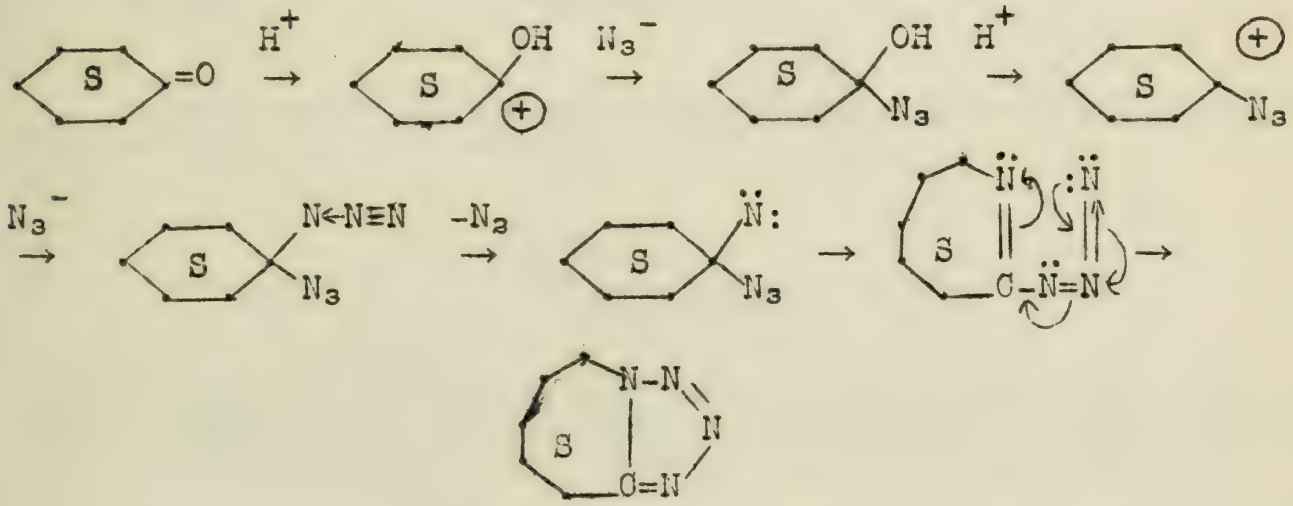
$2,5\text{-}(C_6H_5)_2T$ (7,8)

6.  $+ HO_2CCH{=}NNHC_6H_5 \xrightarrow{NaOEt}$  (9)

7.  $\xrightarrow{N_2H_4}$  $\xrightarrow{HNO_2}$  (10)

8. $C_6H_5NCS + NaN_3 \xrightarrow{CO_2} 1\text{-}C_6H_5\text{-}5\text{-}HS\ T$ (11)

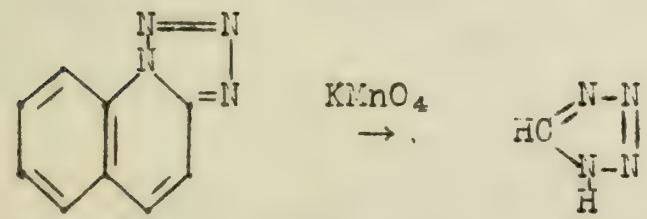
The majority of the tetrazole syntheses may be postulated as involving imido azides as intermediates in the cyclization. Some of these intermediates are stable enough to be isolated. The following mechanisms are suggested:



Metrazole
(Cardiazole)

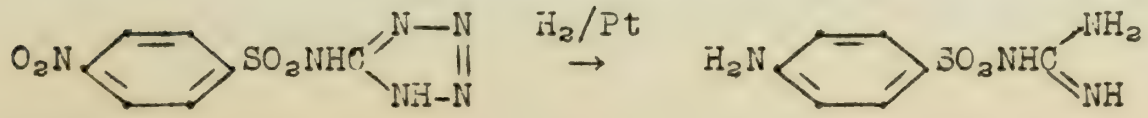
Reactions.--The instability of a number of tetrazoles to heat and shock has led to their successful use as explosives and detonators. Diazotetrazole is perhaps the least stable of these compounds; aqueous solutions explode at 0°C. if more concentrated than two per cent.

Oxidation of the tetrazoles containing sensitive aromatic rings results in degradation to tetrazole. Even:



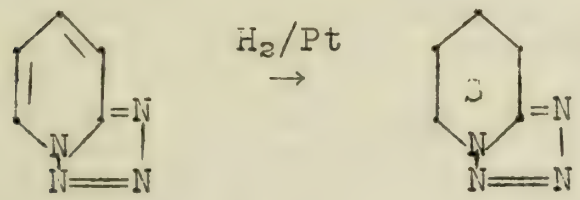
(nearly quantitative) (12)

Reduction may result in disruption of the hetero ring. Thus:



(13)

though many reductions proceed smoothly and without effect on the tetrazole ring.



(14)

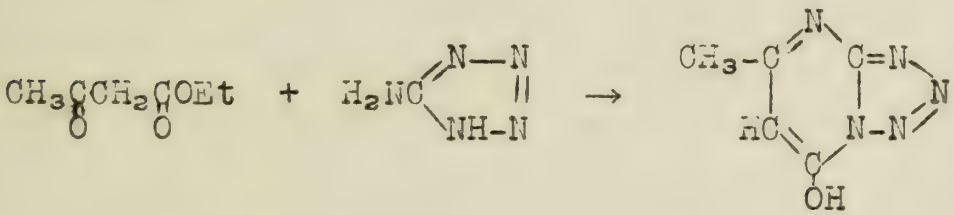
Strong alkalies and acids decompose N-negatively substituted tetrazoles with the evolution of nitrogen.

$$1\text{-}CH_3\ T \xrightarrow{NaOH} CH_3NH_2 + N_2 + NH_3 \qquad (4)$$

5-Phenyltetrazole is unaffected by potassium hydroxide at 240°C. Of interest is the acid decomposition of metrazole yielding pentamethylenediamine, carbon dioxide and nitrogen (15).

Substituents in the 5-position resemble those in the corresponding 2-pyridyl compounds. Decarboxylation of some 5-tetrazole carboxylic acids occurs with unexpected ease. 5-Aminotetrazole may be diazotized and the diazonium salts decomposed by the cuprous halides. Potassium 5-tetrazole sulfonate yields 5-hydroxytetrazole upon fusion with potassium hydroxide.

Condensations of tetrazole with β-diketones and β-ketoesters yield condensed ring heterocyclics. The reaction is analogous to that of phenylhydrazine with the acylacetic esters.



(16)

Uses.--Metrazole is perhaps the best known tetrazole and is extensively employed as a general cardiac and respiratory stimulant. The use of the heavy metal salts of tetrazole, tetrazoyl azide, azotetrazole and others as explosives and initiators is described at length in the literature. To date, no sulfonamido- or sulfanilamidotetrazoles have been reported which were useful as bacteriostatic agents (17).

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General

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Reported by R. E. Heckert
October 24, 1947

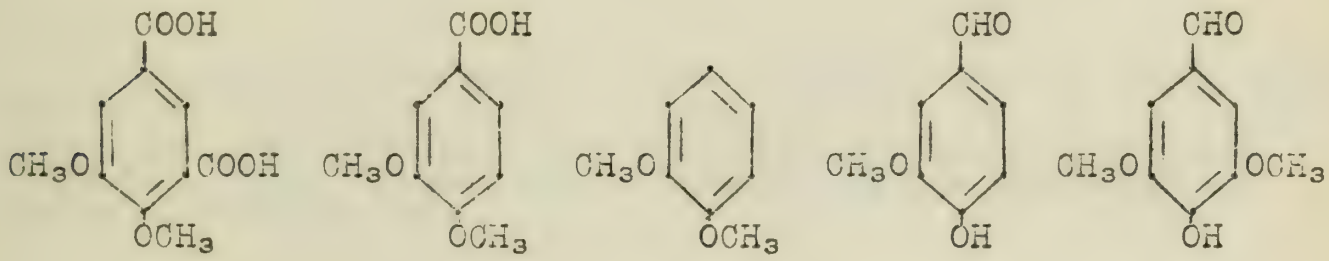
RECENT STUDIES ON THE STRUCTURE OF LIGNIN

I. General.--Lignin is a polymeric substance which binds together the cellulose fibers of woody plants. Because it is produced by the paper industry in huge quantity, its structural formula has been sought after for nearly seventy-five years. In the future it may be a source of aromatic compounds which will rival coal tar and petroleum. Gymnosperm lignin differs from angiosperm lignin, and this fact has been applied to the taxonomic classification of plants.[1] Lignin is probably a mixture of polymers which vary in molecular weight from 3,000 to 10,000 or more.[2]

II. Chemical Structure.--All evidence indicates that lignin contains a benzene ring to which are attached propyl, methoxyl, and hydroxyl groups.[3,4,5] Chemical evidence is not so conclusive that a carbonyl and an ethylene group are present.[6,7] Ultraviolet absorption spectra indicate that lignin is aromatic and has a carbonyl or ethylene group conjugated with the aromatic nucleus.[8]

III. Degradation Studies.--

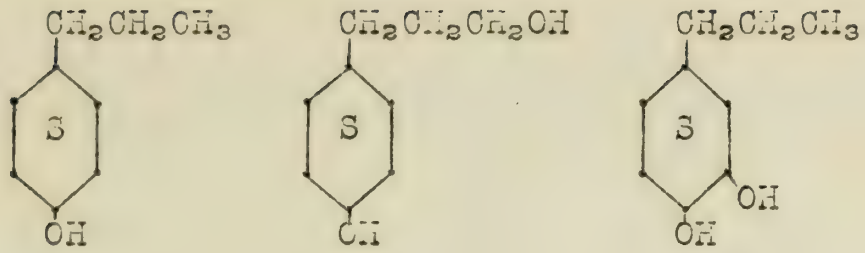
A. Oxidation. Freudenberg's permanganate oxidation of methylated lignin gave isohemipinic acid (I), veratric acid (II), and veratrole (III).[9] Hibbert obtained vanillin (IV) with gymnosperm lignin and vanillin and syringaldehyde (V) with angiosperm lignin by sodium hydroxide-nitrobenzene oxidation.[10]



I II III IV V

B. Alcoholysis. Although Hibbert has identified many compounds of the methoxy-hydroxy-n-propylbenzene type by treating lignin with ethanolic hydrogen chloride, it is likely that all of them were formed from one parent monomer during degradation.[11]

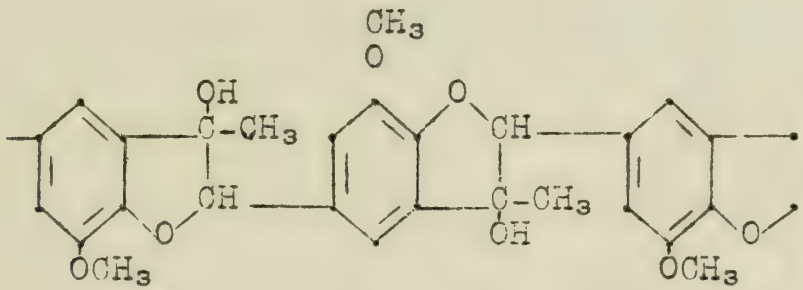
C. Catalytic Hydrogenolysis. Copper chromite catalyzed hydrogenolysis of lignin has given 4-propylcyclohexanol (VI), 3-(4-hydroxycyclohexyl)propanol (VII), 4-n-propylcyclohexanediol-1,2 (VIII), and traces of other products.[12]



VI VII VIII

D. Other Methods. Alkali fusion has produced catechol and protocatechuic acid. Dry distillation at reduced pressure gave eugenol, guaiacol, and vanillic acid.

IV. Proposed Structure.--There has been a number of elaborate guesses of the structure of lignin. The most satisfactory formula suggested until now has been that of Freudenberg (IX).[13]



IX

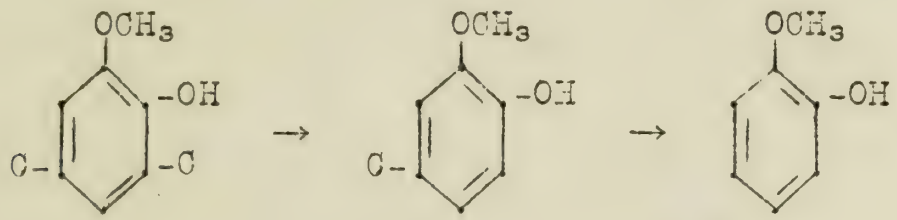
Although Hibbert never committed himself on the total lignin structure, he thought β-oxyconiferyl alcohol (X) was the lignin progenitor and a key compound in a plant oxidation-reduction system.[14] This "Hibbert System" parallels the Szent-Gyorgyi System in animals.[15]

X

V. Synthesis.--Hibbert obtained the first "lignin-like" product. He polymerized both 3-hydroxy 1-(4-hydroxy 3-methoxyphenyl) 1-propanone and 3-hydroxy 1-(4-hydroxy 3-methoxyphenyl) 2-propanone in good yield.[16]

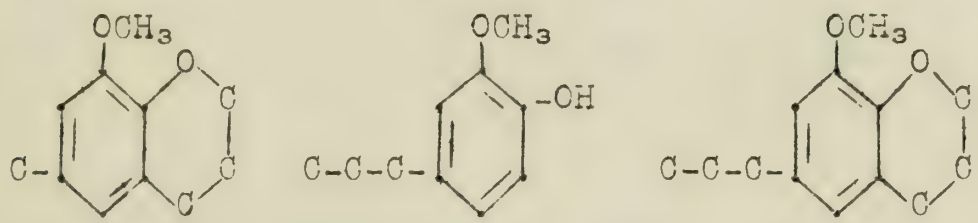
Alfred Russell appears to have successfully completed a synthesis of gymnosperm lignin.[17] He reasoned as follows: Since

isohemipinic acid (I), veratric acid (II), and veratrole (III) have been identified from methylated lignin, and vanillin 5-carboxylic acid, vanillin, and guaiacol are obtained from lignin, clearly the changes XI → XII → XIII take place during degradation.



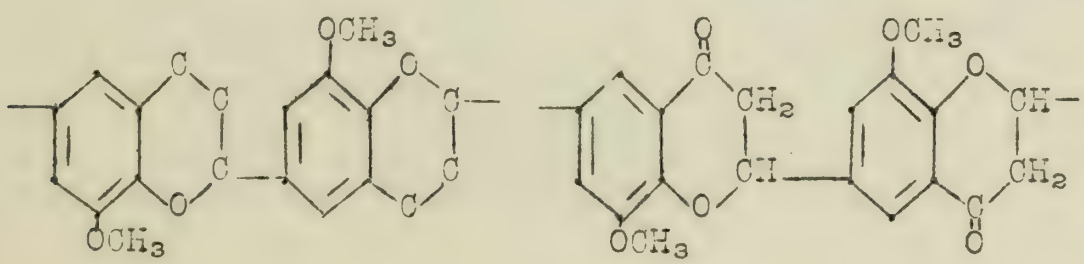
XI XII XIII

One of the free carbon atoms in XI must be attached to at least one other carbon atom in the original lignin. Thus it seems likely that a benzopyran structure (XIV) may exist since a hydroxyl group is ortho to one free carbon. Inasmuch as compounds obtained by alcoholysis have general structures like XV, one might expect the propyl group to be in the position as shown in XVI. Usually



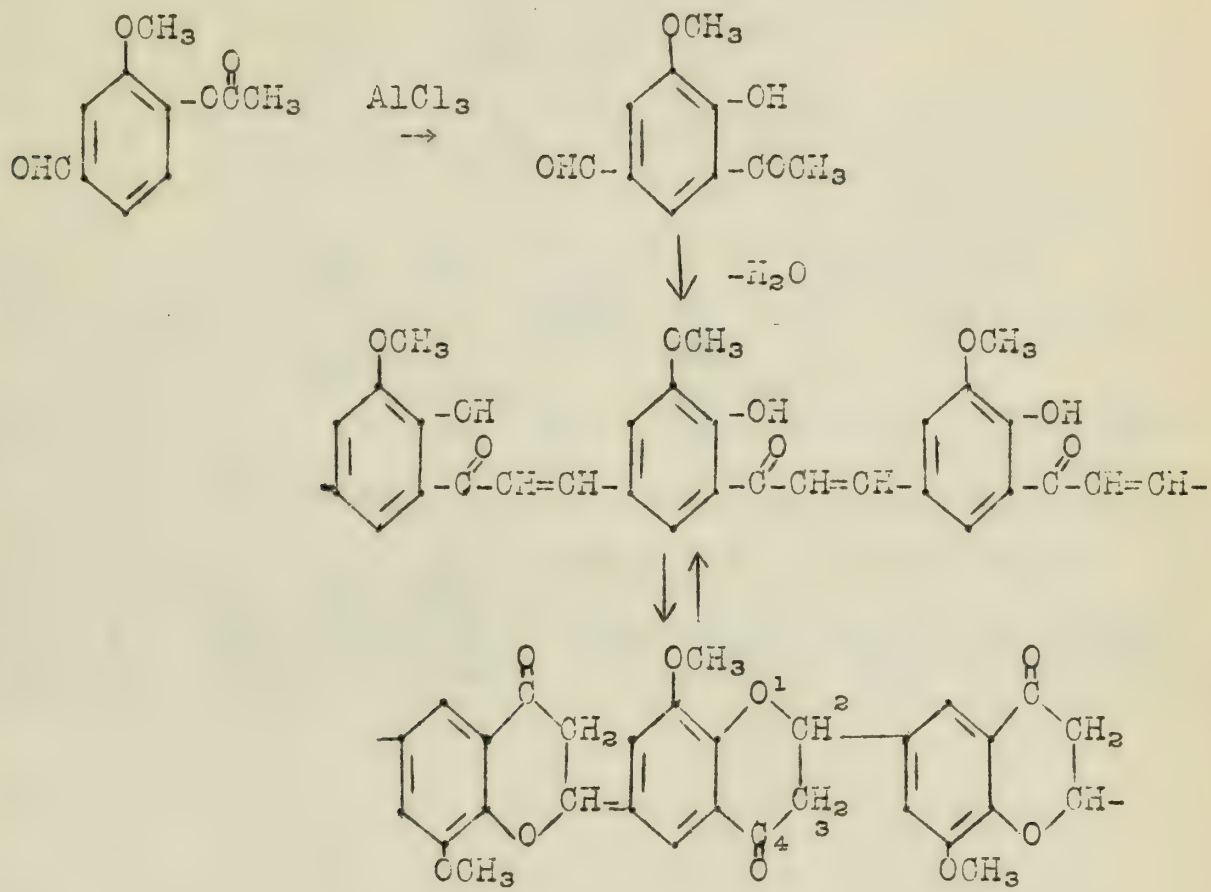
XIV XV XVI

naturally occurring polymers do not have extremely complex monomers. Russell guessed that the three carbons para to the pyranose oxygen form a second pyran ring as in XVII. Expanding this to account for hydrogen and oxygen content of lignin gives XVIII, which is Russell's proposed structure.



XVII XVIII

Russell has synthesized the above polymer by the following method:



The synthetic product (like natural lignin) is soluble in warm aqueous sodium bisulfite. This corresponds to the formation of the sodium salt of a stable sulfonic acid by 1,4-addition to the open-chain form. The hydrogenolysis method will reduce the carbonyl group first. Further hydrogenation under the drastic conditions used amounts to "cracking" in the presence of hydrogen, and cleavage occurs between C_4 and the ring. Acetylation of the synthetic material gives an acetyl value comparable with the natural lignin. This corresponds to an acetyl group on each C_4 enolic group in the pyranose form. Methylation must occur in the open-chain form which is favored by the alkaline conditions employed. The methoxyl value of the synthetic is less than the accepted value for lignin but this may be due to the fact that $AlCl_3$ is an effective demethylating agent. Quantitative halogenation studies show close agreement between synthetic and natural product. Finally, x-ray diffraction spectra of the synthetic material and natural spruce lignin are identical.

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Reported by Roger E. Beyler
October 24, 1947

THE PREPARATION OF α-AMINO ACIDS THROUGH α-OXIMINO ACIDS

Methods of Synthesis of the α-Oximino Acids

Introduction.--The α-oximino acids have long been known. They were used in the synthesis of α-amino acids as early as 1880 (17). Now due to the recent interest in α-amino acids, it is important to investigate all possible courses leading to their synthesis. Though not new, the synthesis of α-amino acids through α-oximino acids has only recently been exploited. The most important features in this synthesis are to be described.

From α-keto acids.--A convenient method for making the α-oximino acids is through the keto acid and hydroxyl amine. By this means, α-oximino propionic acid (1), and others (2,3) have been made. Likewise, α-oximino acids have been made from α-thioketo acids (25). Both of these syntheses are the conventional reactions of keto or thioketo groups with hydroxyl amine and need not be further described.

From aldehydes with one less carbon atom.--α-Oximino acids have been prepared by treating an aldoxime with hydrogen cyanide followed by oxidation with strong sulfuric acid. α-Oximino butyric acid, and other oximino acids, have been made in this way (4).

$$CH_3CH_2CH{=}NOH + HCN \rightarrow CH_3CH_2CH(NHOH)CN \xrightarrow{H_2SO_4}$$

$$CH_3CH_2C(=NOH)CONH_2 \rightarrow CH_3CH_2C(=NOH)COOH$$

From α-halogen esters.--α-Bromoesters upon treatment with sodium nitrite in solution with long standing yield the corresponding oximino ester. In this way, α-oximino propionic acid was made (5). In a similar manner, the α-bromoacid can be treated with hydroxylamine by which several α-oximino acids have been made (6).

From unsubstituted β-keto esters.--The reaction of an unsubstituted β-keto ester and nitrous acid yield an α-oximino-β-keto ester which upon reduction results in an α-amino-β-hydroxy ester (7,8,9,10). The intermediate used in the synthesis of threonine was prepared in this way.

$$CH_3COCH_2COOEt + HNO_2 \rightarrow CH_3COC(=NOH)COOEt + H_2O \quad 65\%)$$

From α-substituted-β-keto esters.--The reaction of α-substituted-β-keto esters with potassium nitrite may take two courses (11). If the keto ester is treated with potassium nitrite and excess potassium hydroxide in water, an oximino ketone is formed, but if the keto ester is treated with alcoholic potassium hydroxide followed by an excess of nitrous acid, the α-oximino ester is obtained.

$$CH_3COCH(CH_3)COOEt \begin{cases} + KNO_2 + KOH + H_2O \rightarrow H_3CCOC(=NOH)CH_3 + CO_2 \\ + \text{alc. } KOH, HNO_2 \rightarrow CH_3C(=NOH)COOEt + CH_3COOH \end{cases}$$

Of more practical value is the reaction of alkyl substituted acetoacetic esters with an alkyl nitrite in either acids (16) or bases (21) to yield the corresponding α-oximino acid, or by the use of nitrosyl sulfuric acid (26).

$$CH_3COCH(CH_3)COOEt + O_2NSO_3H \text{ or } [BuNO_2 + (H_2SO_4 \text{ or } NaOEt)] \rightarrow$$

$$CH_3C(=NOH)COOEt(75 \text{ to } 80\%) + CH_3COOH$$

The ease of replacement of the acyl group in these reactions has been shown to decrease in this order $-CHO$, $-COCH_3$, $-COC_6H_5$ (12). A large excess of the nitrite is to be avoided since it is known to cause the formation of the α-keto acid (13).

$$RC(=NOH)COOR' + (XS)\ HNO_2 \rightarrow RCOCOOR' + 4NO + 2H_2O$$

From malonic acids and esters.--When alkyl substituted malonic esters or acids are treated with alkyl nitrites in either acid or basic solution, α-oximino acids are produced (14,15,16).

$$CH_3CH_2CH(COOH)_2 + HCl \text{ or } NaOEt \xrightarrow{BuNo} CH_3CH_2C(=NOH)COOH\ (60 \text{ to } 80\%)$$

$$+ CO_2 + H_2O$$

If the unsubstituted malonic ester is similarly treated, oximino malonic ester is obtained which has been used in the synthesis of several amino acids (23,24).

$$CH_2(COOEt)_2 + BuNO_2 + NaOEt \rightarrow HON{=}C(COOEt)_2 \quad 87\%$$

Methods of Reducing α-Oximino Acids

Metal-acid combinations.--Tin and hydrochloric acid (17), zinc and hydrochloric acid (8), sodium amalgam (2), aluminum amalgam (13) and sodium in alcohol (14) have all been tried with varying degrees of success, but have been abandoned in view of recent developments in catalytic hydrogenations.

Catalytic hydrogenations.--Platinum oxide and hydrogen was used to reduce α-oximino glutaric acid to glutamic acid. The yield was 39% starting from diethyl α-acetylglutarate. By using

palladium dispersed on activated charcoal (19) with a trace of hydrochloric acid, the following amino acids were prepared: alanine 75%, α-amino-n-butyric acid 78%, norvaline 83%, norleucine 85%, isoleucine 80%, aspartic acid 60%, glutamic acid 74%, phenylalanine 89%, o-methyl tyrosine (85%) (16). Raney nickel and hydrogen at 300 atm. was used in the preparation of threonine (9). A two-stage reduction using first palladium on charcoal with a trace of hydrochloric acid followed by a reduction using platinum with a trace of ferric chloride was found necessary in the preparation of a hydroxy glutamic acid (21).

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Reported by Viron V. Jones
October 31, 1947

STEREOCHEMISTRY OF ANSA-COMPOUNDS

I. General.--The name "ansa-compounds" has been applied by Lüttringhaus (5) to those compounds which contain an aromatic ring bridged by a polymethylene "handle" joining positions other than ortho or peri. Ansa-compounds which have been studied include certain octa-, deca-, and dodeca-methylene derivatives of hydroquinone, resorcinol, 1,5- and 2,6-dihydroxy- and 1,5-dithionaphthalenes, and p-phenylenediamine.

II. Stereochemistry.--This class of compounds is of great stereochemical interest, since when free rotation is hindered the molecules may be asymmetric, although there are no asymmetric atoms. The existence of an ansa-compound in optically active forms depends upon the following factors:

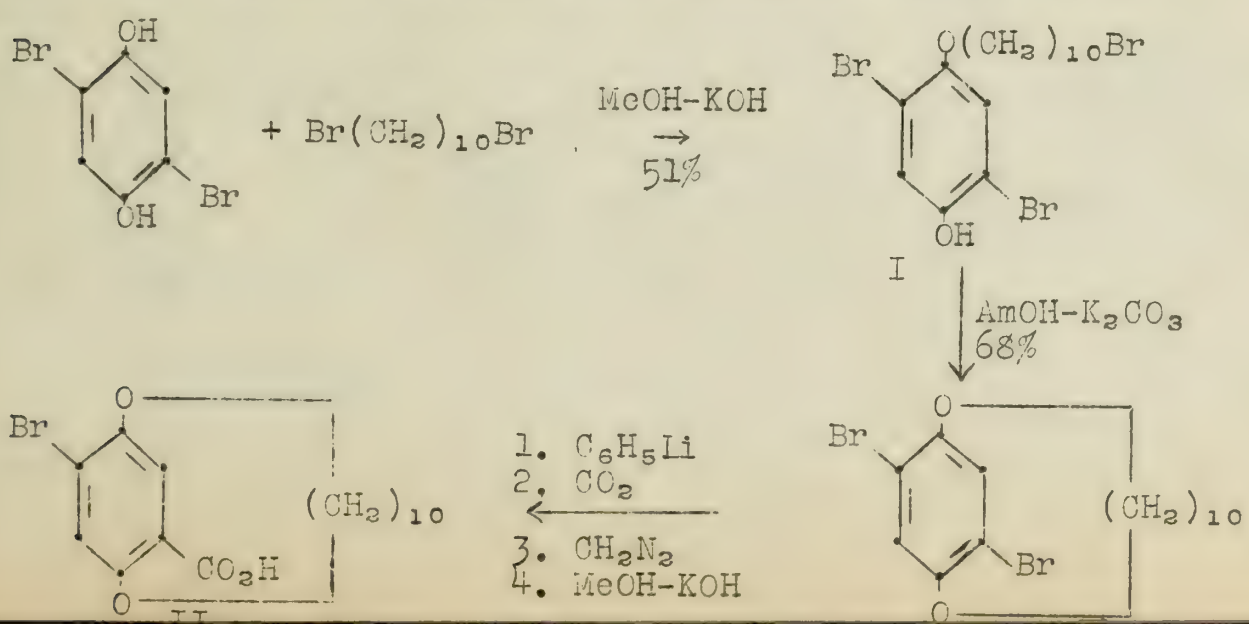
1. Length of the polymethylene chain.
2. Presence and size of blocking groups on the aromatic ring.
3. Position of substituents on the aromatic ring.

The first two requirements are interdependent, and together prevent free rotation of the polymethylene bridge about the aromatic ring; the third prevents the existence of a plane of symmetry.

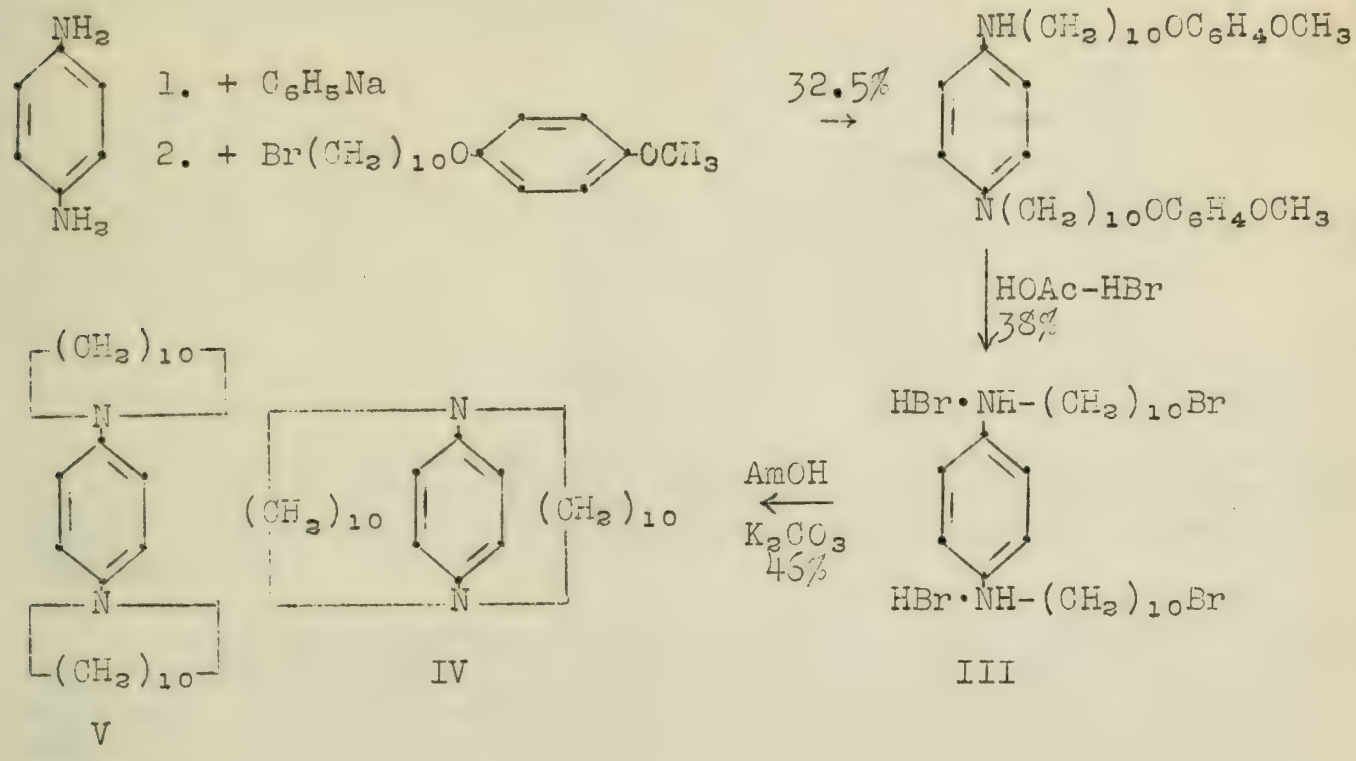
It has been found that an octamethylene bridge is too small to rotate freely about an unsubstituted benzene ring. The size of the decamethylene bridge is such that large blocking groups are necessary to prevent rotation. A dodecamethylene bridge is large enough to rotate freely past a bromo-substituent on the benzene ring.

III. Synthesis.--In general, the synthesis of ansa-compounds depends upon the application of the dilution principle to produce intra- rather than inter-molecular reaction of the intermediate half-ether (I) or di-secondary amine (III).

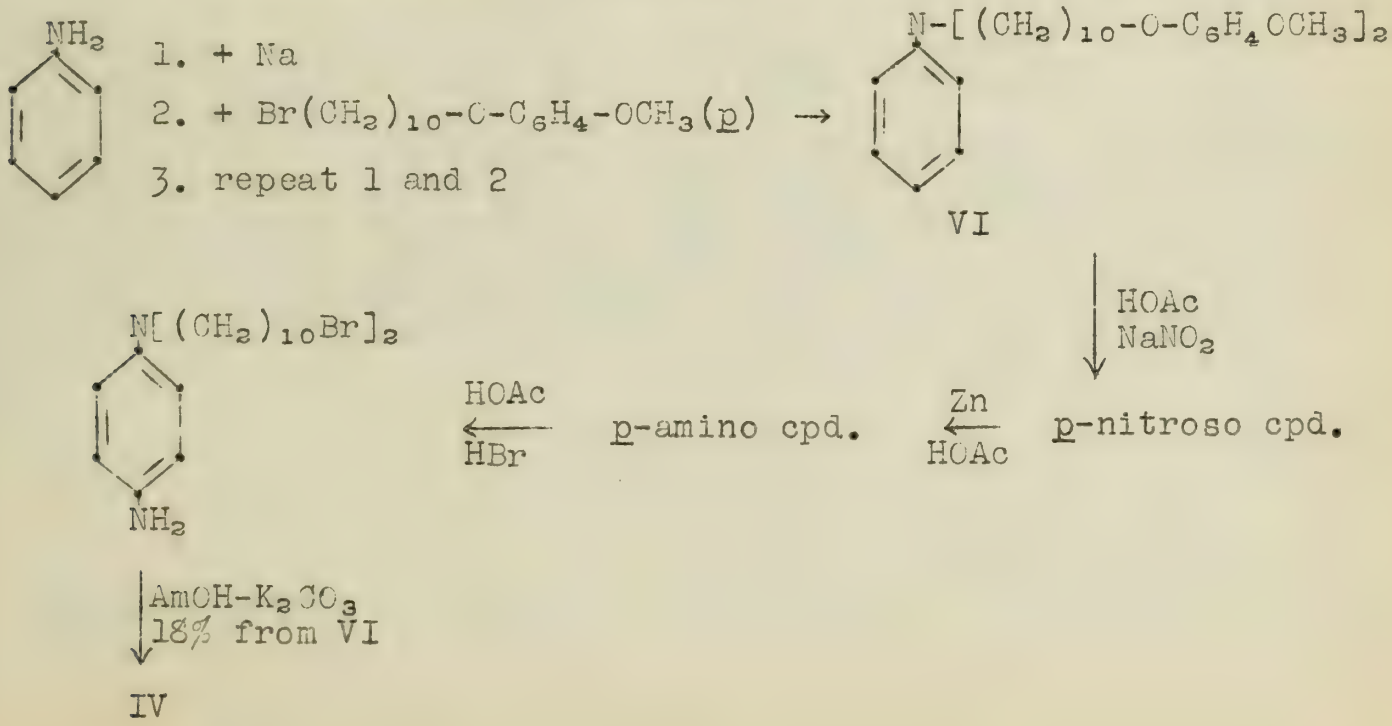
A. Ethers (2,3,4,5,7).--A typical synthesis is that of 2-bromo-5-carboxy-1,4-phenylene decamethylene ether (II).



B. Amines (8).--N,N,N',N'-Bis-decamethylene-p-phenylenediamine (IV) is the only compound of this type which has been synthesized:

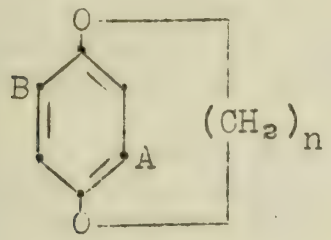


This synthesis does not establish the structure of the product, since the ring closure might have resulted in the isomeric tricyclic system V. Proof that the compound IV is the actual product was obtained by synthesis of this compound by a second method:



IV. Optical Activity (4,5,6,7).--

A. Resolution.--The following compounds have been isolated in optically active form:



	A	B	n
III	Br	CO_2H	10
VII	Br	CO_2CH_3	10
VIII	Br	$NHCOCH_3$	10
IX	Br	NH_2	10
X	Br	Br	10
XI	H	CO_2H	8
XII	H	CO_2CH_3	8

Compounds III and XI were resolved by conversion to the cinchonine and strychnine salts. The remaining compounds were synthesized as the active form, starting from an active form of Compound III.

B. Racemization.--Experiments on Compounds III, VII, XII have shown that the active forms of ansa-compounds are extremely stable to racemization. Compounds VII and XII were heated two or more hours at 200°, while the sodium salt of III was heated with aqueous NaOH for three hours at 100°. In all cases there was complete retention of optical rotation.

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Reported by Ruth C. Pierle
October 31, 1947

RECENT ADVANCES IN THE FORMATION OF LARGE RINGS

The proof by L. Ruzicka in 1926 that the naturally-occurring compounds, muscone and civetone, were macrocyclic ketones led to extensive research on the general problem of synthesizing macrocarbocycles. A previous seminar[1] has outlined the contributions to this problem up to the year 1945. Since that time several new methods have been devised and further work has been done on the methods already known.

H. Hunsdiecker[2] has extended his synthesis of civetone to include both the α- and β-forms. The α-form is probably <u>trans</u> and the β-form <u>cis</u>.

$$HO(CH_2)_6CHOHCHOH(CH_2)_7COOH \xrightarrow[AcOH]{HBr} Br(CH_2)_6CHBrCHBr(CH_2)_7COOH \xrightarrow{Zn}$$

$$Br(CH_2)_6CH{=}CH(CH_2)_7COOH \xrightarrow[MeOH]{HCl} Br(CH_2)_6CH{=}CH(CH_2)_7COOMe \xrightarrow[Na]{M.E.}$$

$$(ROOC)_2CH(CH_2)_6CH{=}CH(CH_2)_7COOMe \xrightarrow{KOH} \xrightarrow[\triangle]{H_3O^+} \alpha\ HOOC(CH_2)_7CH{=}CH(CH_2)_7COOH$$

$$\xrightarrow[AcOH]{H_2O_2} HOOC(CH_2)_7CHOHCHOH(CH_2)_7COOH \xrightarrow[AcOH]{HBr} HOOC(CH_2)_7CHBrCHBr(CH_2)_7COOH$$

$$\xrightarrow{Zn} \beta\ HOOC(CH_2)_7CH{=}CH(CH_2)_7COOH$$

$$\alpha \text{ or } \beta\ HOOC(CH_2)_7CH{=}CH(CH_2)_7COOH \rightarrow CN(CH_2)_7CH{=}CH(CH_2)_7CN \xrightarrow{\emptyset NEtLi}$$

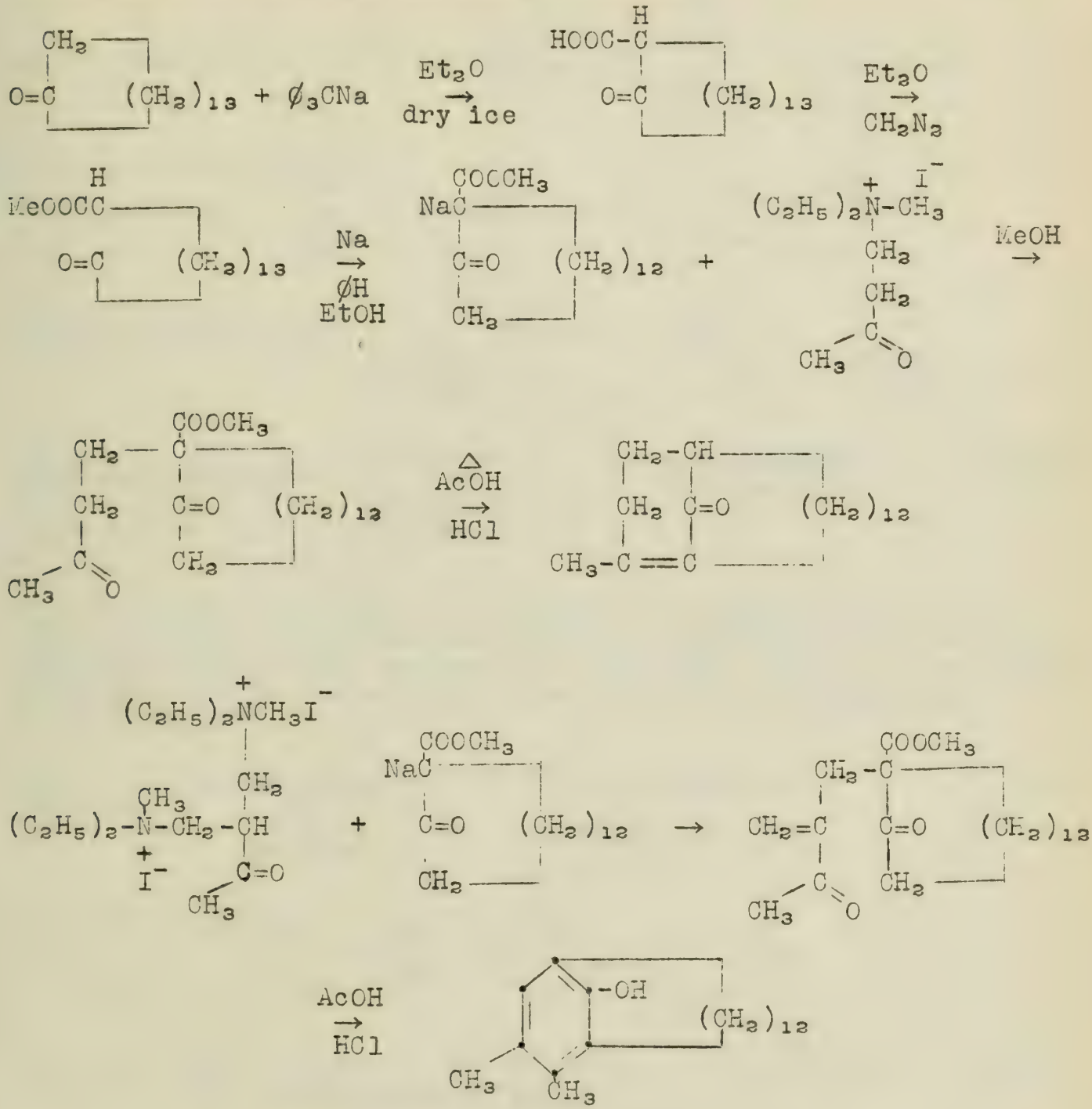
$$\xrightarrow{H_3O^+} \alpha \text{ or } \beta \begin{array}{l} CH(CH_2)_7 \\ \| \qquad\quad C{=}O \\ CH(CH_2)_7 \end{array} \quad \text{(civetone)}$$

Industrial exploitation of the decomposition of salts of polymethylene-α,ω-dicarboxylic acids, Ruzicka's original method for the synthesis of large rings, has made possible a study of this reaction by M. Stoll and A. Rouvé.[3] They have reported yields of semicarbazones of the ketone from thapsic acid salts of metals ranging from Li to U. The greatest yield was obtained from the trivalent cerium salt (10%).

$$(C_{16}H_{28}O_4)_3Ce_2 \xrightarrow{\triangle} CO_2 + Ce_2O_3 + \boxed{(CH_2)_{14}\ C{=}O} + O{=}C\begin{array}{l}\ulcorner (CH_2)_{14} \urcorner \\ \qquad\qquad C{=}O \\ \llcorner (CH_2)_{14} \lrcorner\end{array}$$

$$+ \left\{ OOC\text{-}\left[(CH_2)_{14}\text{-}CO\right]_n\text{-}(CH_2)_{14}\text{-}COO \right\}_3 Ce_2$$

The following bicyclic compounds with a polymembered ring were prepared by V. Prelog, M. M. Wirth, and L. Ruzicka[4] using cyclopentadecanone as a starting material.



Recently H. Hunsdiecker[5] has introduced a new type of ring closure in which he obtained 9- to 17-membered lactones in yields ranging from 56.3 to 96.8% by cyclizing ω-halogen acids with K_2CO_3 in methyl ethyl ketone solution, utilizing Ruggli's high dilution principle.

$$HOCO(CH_2)_8COOH \xrightarrow[MeOH]{Ba(OH)_2} Ba_{\frac{1}{2}}OCO(CH_2)_8COOMe \xrightarrow[AgNO_3]{KOH}$$

$$AgOCO(CH_2)_8COOMe \xrightarrow[Br_2]{CCl_4} Br(CH_2)_8COOH \xrightarrow[\text{M.E.K. 48 hrs.}]{\substack{88^\circ \\ K_2CO_3}} CH_2(CH_2)_7C{=}O \quad (56.3\%)$$

$$I(CH_2)_7COOCH_3 \xrightarrow[Cu\cdot Zn,\ \Delta]{\text{toluene HAc}} Zn(CH_2)_7COOCH_3 \xrightarrow[\text{toluene}]{Br(CH_2)_7COCl}$$

$$Br(CH_2)_7\underset{\underset{O}{\|}}{C}(CH_2)_7COOH \xrightarrow[\text{M.E.K. 336 hrs.}]{K_2CO_3} CH_2(CH_2)_6\underset{\underset{O}{\|}}{C}(CH_2)_7C{=}O \xrightarrow[FeSO_4,\ EtOH]{PtO_2}$$

(70%)

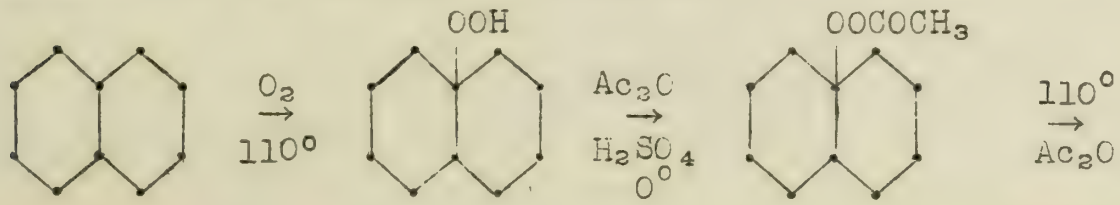
$$CH_2(CH_2)_6\underset{OH}{C}(CH_2)_7C{=}O \xrightarrow[\text{silica gel, } 260\text{-}280^\circ]{H_4P_2O_7 \text{ on}} \text{isomeric hexadecene 1,16-lactones} \quad (40\text{-}50\%)$$

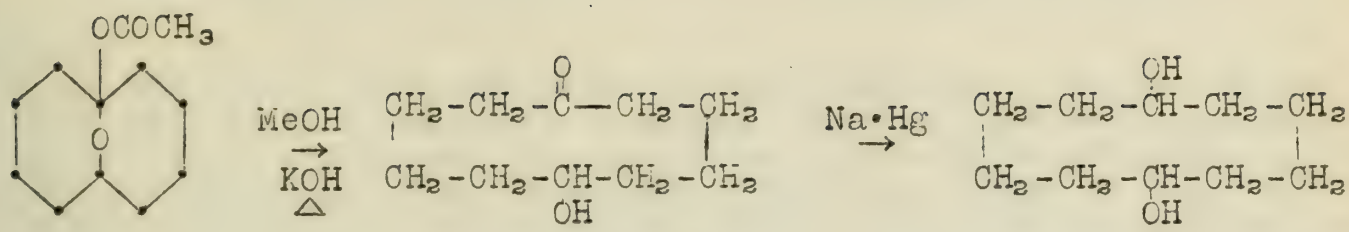
Another new method for synthesizing many-membered carbon rings involves the self-condensation of bifunctional ketenes at high dilution to form macrocyclic diketenes, readily convertible to many-membered carbocyclic ketones (A. T. Blomquist and R. D. Spencer[6]).

$$(C_2H_5)_3N \quad ClOC(CH_2)_8COCl \xrightarrow[\text{42 hrs.}]{EtO_2} \begin{matrix} O{=}C{=}CH(CH_2)_6\text{-}CH_2C{=}O \\ | \\ O{=}C{=}CH(CH_2)_6\text{-}C{=}C{=}O \end{matrix} \rightarrow$$

$$\begin{matrix} O{=}C{=}C(CH_2)_6CH_2\text{-}C{=}O \\ | \qquad\qquad\qquad | \\ O{=}CCH_2(CH_2)_6\text{-}C{=}C{=}O \end{matrix} \xrightarrow[EtOH]{KOH} \xrightarrow{H_3O^+} O{=}C\begin{matrix}(CH_2)_8 \\ (CH_2)_8\end{matrix}C{=}O$$

R. Criegee[7] has used the following new method in obtaining members of the cyclodecane series.





The Reppe[8] synthesis has also yielded some interesting macrocyclic compounds.

$C_2H_2 \xrightarrow{Ni(CO)_4}$ cyclo8ctatetraene, cyclodecapentaene, and cyclododecahexaene

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Reported by Russell Gilkey
October 31, 1947

THE SCOPE AND LIMITATIONS OF THE PFITZINGER REACTION

The reaction consists of the condensation of isatic acid with ketones. In addition to simple ketones, keto-ethers, keto acids, cyclic ketones, the isonitroso derivatives of ketones, and acids containing active methylene groups are known to react to produce substituted cinchoninic acids. Quinoline derivatives are readily available upon decarboxylation of these acids by heat.

In 1944 Buu-Hoi started an investigation of the steric hindrance effects in this reaction. First he varied the substituents near the α-methylene and carbonyl groups of the ketone. Using isatin itself in studying the ketone series $ArCO(CH_2)_nCH_3$ he found:

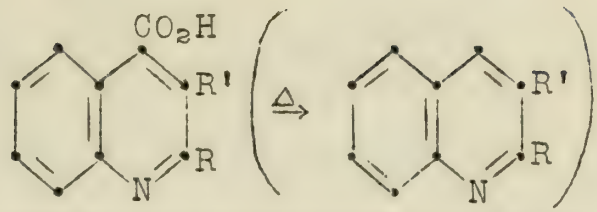
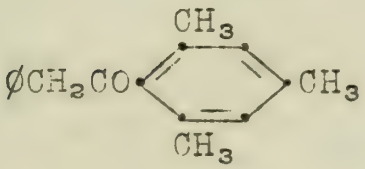
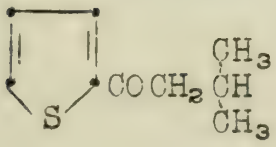
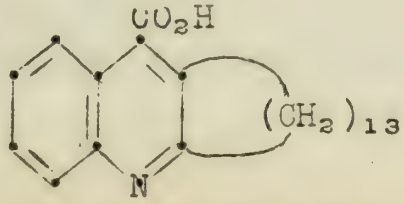
(1) When $n \leq 2$ the reaction proceeds readily; when $n > 2$ (3 to 16) there is no reaction.
(2) Ar may be varied at will.
(3) <u>Ortho</u> substitution in the aromatic ring impedes the reaction in most cases. When the ring is phenyl or thienyl <u>ortho</u> substitution has no effect. When the ring is naphthyl or thianaphthyl, groups larger than methyl or methoxyl in the <u>ortho</u> position prevent reaction.
(4) Large groups attached to the α-methylene carbon atom together with <u>ortho</u> substitution prevent reaction.

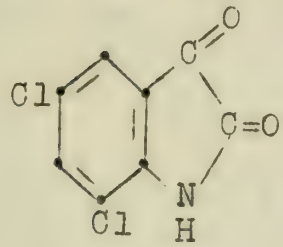
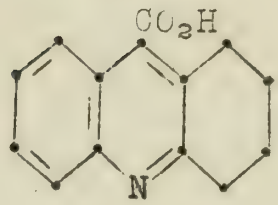
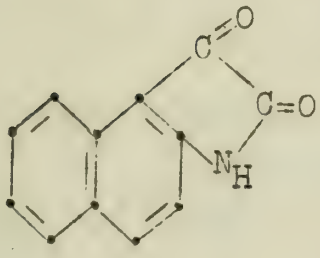
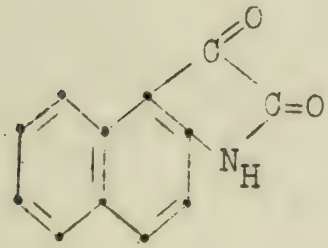
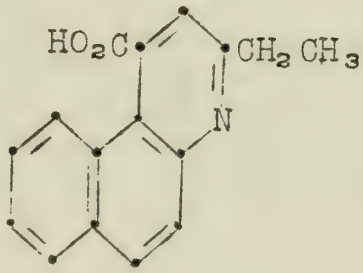
In all cases so far observed where no reaction occurs with isatin, the ketone bears substituents near both functional groups. Thus camphor and menthone fail to condense. 3-Methylcyclohexanone gives exclusively the 2-methyltetrahydroacridine product in a 50% yield while 4-methylcyclohexanone gives the corresponding reaction with a 70% yield.

Detailed investigation of the two series $R(CH_2)_kCO(CH_2)_mR'$ and $ArCO(CH_2)_nAr'$ has not been carried out. Steric hindrance effects should be similar to those above in the first series. Buu-Hoi has done a little work with the second series and has reported that the reaction is normal when n = 1, and the aryl groups are phenyl, thienyl, naphthyl, or thianaphthyl.

Using unhindered ketones to investigate the effect of substituents in the isatin molecule it was observed that in all cases the condensation proceeds normally.

When steric hindrance occurs in both molecules then the reaction either fails entirely or takes an abnormal course. Thus pulegone first produces acetone which in turn condenses readily. α- and β-naphthisatins will condense only with methyl ketones. Increasing the molecular weight of the ketone in itself has no effect on the reaction as is shown by the reactions between α- or β-naphthisatin and such polynuclear ketones as 2-acetylfluorene, 3-acetylpyrene, and 2-acetylchrysene.

No.	Isatin and Ketones	Products 	Ref.
1	$CH_3COCH_2CH_3$	R = R' = $-CH_3$	14,15
2	$CH_3COCH{=}NOH$	R = $-CH{=}NOH$, R' = $-H$	14
3	$CH_3COCH_2CO_2H$	R = $-CH_3$, R' = $-CO_2H$ not decarboxylated	14
4	α-$C_{10}H_7OCH_2$ | $COCH_3$	R = $-CH_3$, R' = α-$C_{10}H_7O$-	6
5	H_2C-$S\phi$ | $O{=}C$-CH_3	R = $-CH_3$, R' = $-S\phi$	11
6	$\phi COCH_2\phi$	R = R' = $-\phi$	2,14
7	ϕCH_2CO_2H	R = $-OH$, R' = $-\phi$	9
8	β-$C_{10}H_7C{=}O$ | $(CH_2)_2CH_3$	R = β-$C_{10}H_7$-, R' = $-CH_2CH_3$	2
9	β-$C_{10}H_7C{=}O$ | $(CH_2)_3CH_3$	N. R.	2
10		N. R.	2
11		R =  , R' = $-CH(CH_3)_2$ Poor yield	1,5
12	$(CH_2)_{14}$ C=O	 not decarboxylated	3
13	ϕCH_2COCH_3	R = $-CH_2\phi$, R' = $-H$	1

No.	Isatin Derivative	Ketone	Product	Ref.
14				3
15			N. R.	4
16		$CH_3COCH_2CH_3$		3

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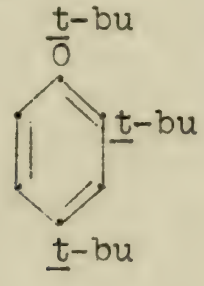
Reported by J. H. Boyer
November 7, 1947

HINDERED PHENOLS

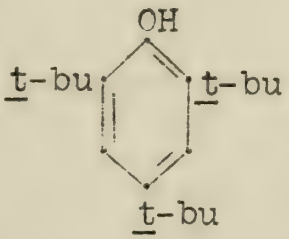
History--Many phenols are rendered insoluble in aqueous alkali by the introduction of various groups into the benzene ring. In 1919 Adams (1) published a paper on the phenylhydrazones of various o-hydroxyaldehydes and ketones in which he advanced the theory that their insolubility in aqueous alkali arose from their extreme insolubility in water, coupled with their very slight dissociation. In the same and in subsequent years Claisen (2,3) described several alkyl, alkenyl, and benzyl phenols which were insoluble in aqueous alkali. Since the publication of Claisen's work much interest has been shown in the preparation of these ortho substituted phenols, called cryptophenols, because their very slight acidity decreases their toxicity but not their antiseptic value.

Present methods of preparation of these phenols include the condensation of phenols with alcohols, alkyl halides, aldehydes, acids, and acid chlorides; the rearrangement of phenyl ethers to the isomeric phenols; and the condensation of phenols with monoethylenic compounds. All the cryptophenols have the common properties of being very weakly acidic, being practically insoluble in aqueous alkali, being soluble in a methyl alcohol solution of potassium hydroxide, called Claisen's solution, and giving a positive test with aqueous or alcoholic ferric chloride solution (4,5,6,7,8,9). Stillson, Sawyer, and Hunt (10) have recently synthesized a large number of phenols which are insoluble even in absolute Claisen's solution and give no ferric chloride test.

Hindrance of Tributylphenol--The first of this type of compound prepared was 2,4,6-tri-t-butylphenol. Gaseous isobutylene was passed into phenol at 50-60° in the presence of a catlytic amount of sulfuric acid. A white crystalline product was obtained in high yield which was insoluble in both aqueous and alcoholic alkali solutions. This condensation product had an empirical formula $C_{13}H_{30}O$ which would correspond to either:



or



Since both alkyl phenols and phenyl alkyl ethers had been reported to result from the addition of olefins to phenols in the presence of sulfuric acid, the ether was assumed to have been formed. All attempts to rearrange the suspected ether to the trialkylphenol failed. However, a Friedel-Crafts synthesis condensing t-butyl chloride on phenol in the presence of aluminum chloride produced a compound identical with the condensation product of isobutylene and phenol. This strongly indicated a phenolic structure. Metallic sodium had no effect on an anhydrous petroleum ether solution of the compound, but a liquid ammonia solution of the compound took up one equivalent of the metal. A Zerewitinoff

determination showed one replaceable hydrogen to be present. A benzoate was prepared by shaking an anhydrous diethyl ether solution of the compound with sodium-potassium alloy and treating the mixture with benzoyl chloride. Thus the compound was shown to be a very inactive phenol.

Other examples--Since it had long been supposed that the insolubility of the cryptophenols was due to the steric hindrance of the large ortho substituents, these very inactive phenols were called the hindered phenols. All compounds synthesized that had both ortho positions occupied by either a t-butyl or a t-amyl group were found to be hindered phenols with the same chemical properties as 2,4,6-tri-t-butylphenol.

The hindering effect of large groups in the ortho position has been repeatedly shown. 2,6-Dimethyl-4-t-butylphenol is soluble in 10% sodium hydroxide while its isomer, 2,4-dimethyl-6-t-butylphenol, is not (11). 2,6-Di-t-butyl-4-methylphenol is soluble in absolute Claisen's solution to the extent of 6 g/l. Addition of water to the alcoholic alkali solution precipitates the phenol. 2,4,Di-t-butyl-6-methylphenol is soluble in absolute Claisen's to the extent of 20 g/l. Addition of water causes negligible precipitation, but acidification of the clear solution causes complete precipitation. This shows that the increased solubility of 2,4,di-t-butyl-6-methylphenol is due to its increased solubility in alkali and not to increased solubility in alcohol.

Effect of Hindrance on Hydrogen Bonding.--Coggeshall (12) has made an investigation to determine the effect of large ortho substituted alkyl groups on the hydrogen bonding of phenols. The infrared absorption band for the uncomplexed hydroxyl group lies at 2.7 microns; this is obtained in dilute solutions. In solutions concentrated enough to permit hydrogen bonding this absorption band shifts to 3.0 microns. Measurement of the shift in wave length of this absorption band in going from dilute to concentrated solutions of various phenols were made. Compounds with no or small groups in the ortho positions were found to have a large $\Delta\lambda$; those with a large group in one ortho position and with the other ortho position either open or occupied by a small group were found to have a smaller $\Delta\lambda$; those with both ortho positions occupied with large groups had a very small $\Delta\lambda$ indicating that little hydrogen bonding had taken place. These experiments showed that hydrogen bonding is sterically hindered by large groups in the ortho positions. Large groups on the 3,4, and 5 positions were found to have only a secondary effect.

The compounds that were found to have their hydrogen bonding most sterically hindered are the same compounds that have been termed hindered phenols because of their chemical properties. Variations in hydrogen bonding correspond with variations in chemical properties. Thus, the chemical properties of the hindered phenols and the cryptophenols have been shown due to the steric effects of large ortho groups.

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Reported by R. E. Berry
November 7, 1947

REDUCTION OF ORGANIC COMPOUNDS BY LITHIUM ALUMINUM HYDRIDE

Not long after the discovery of $LiAlH_4$ by Finholt, Bond, and Schlesinger in 1946,[1] it was realized that this compound possessed unique properties as a reducing agent for organic compounds. Prior to this time, attempts were made to use other inorganic hydrides such as NaH,[2] CaH_2,[3,4] LiH,[5] and $AlBH_4$[6] for reductions of organic compounds, but very little success was achieved. The only generally successful use of a hydride for reduction was recently reported by Darzens,[7] who replaced Na by NaH in the Bouveault-Blanc reduction, with an improvement of yields.

Studies in the uses of $LiAlH_4$ in organic chemistry, begun by R. F. Nystrom and W. G. Brown at the University of Chicago, have shown this new compound to be an extremely useful, efficient, and versatile reagent for reductions of organic compounds.[6,8]

Preparation of the Reagent.--$4LiH + AlCl_3 \rightarrow LiAlH_4 + 3LiCl$ In order to prevent a long induction period in the reaction between LiH and $AlCl_3$ it is necessary to use a small quantity of $LiAlH_4$ to initiate the reaction. This may be prepared in impure form by boiling small quantities of LiH and $AlCl_3$ in dioxane and then in ether, followed by evaporation of the solvent. For the preparation of appreciable quantities of the reagent, finely ground LiH (in excess) is added to a solution of a few grams of $LiAlH_4$ in ether. An ethereal solution of $AlCl_3$ is added with stirring at a rate such that boiling is continuous. After filtering the precipitated LiCl and excess LiH, the filtrate contains ca. 85% yield of $LiAlH_4$ and it is used as such.

Use of the Reagent.--The general procedures used are the same as with the Grignard reagent. An ether solution of the compound to be reduced is added slowly to an ether solution of the reagent in a nitrogen atmosphere. After complete reaction has occurred, water is added to decompose the salts, and the precipitated $Al(OH)_3$ is dissolved by dilute H_2SO_4 or NaOH. The product can be isolated from the ether layer merely by removal of the solvent.

One of the most outstanding uses of this new reagent is in the direct reduction of carboxylic acids. A variety of acids have been smoothly reduced to the corresponding alcohols in excellent yields (80-99%).[6] Some examples are benzoic, phenylacetic, trimethyl acetic, stearic, furoic, salicylic, sorbic, anthranilic and sebacic acids.

Anhydrides, acid chlorides, esters, aldehydes, and ketones have also been reduced to the corresponding alcohols with exceptional facility and high yields.[6,8] Several examples are:

Anhydrides - benzoic; phthalic. (87%)

Acid Chlorides - palmityl; isocaproyl; sym.-o-phthalyl; sorbyl. (72-99%)

Esters - Ethyl palmitate, laurate, adipate; methyl oleate; n-butyl malonic ester. (83-98%)

Aldehydes - n-heptaldehyde; crotonaldehyde; p-dimethylaminobenzaldehyde. (85-95%)
and chloral hydrate. (50%)

Ketones - Butanone-2; cyclopentanone, acetomesitylene. (62-100%)

Halogen compounds with active halogen atoms are reduced to hydrocarbons, such as allyl bromide to propene (85%), and cetyl iodide to hexadecane (95%).[6] Nitriles are reduced to amines without formation of 2° or 3° amines.[6] Aromatic nitro compounds are reduced to azo compounds,[6] and quinones are converted to hydroquinones.[6] In general, olefinic double bonds are not reduced except in a few special cases.

Advantages of $LiAlH_4$ as a Reducing Reagent.--

1. It is easily prepared from commercially available LiH.
2. It is stable at room temperature.
3. It is ether soluble.
4. It possesses a favorable ratio of reducing capacity to mass.
5. It can be used at room temperature and without the use of any unusual equipment or techniques.

Disadvantages and Precautions in Use of $LiAlH_4$.--

1. Compounds insoluble in ether do not react well.
2. High cost of LiH.
3. Some active -H substances decompose the reagent.
4. Reactions must be carried out in anhydrous, CO_2-free, nitrogen atmosphere. This is due to the rapid reaction with oxygen and the formation of explosive complexes with CO_2.[9]

Work is now in progress on the mechanism of the reduction reaction and the use of $LiAlH_4$ in the determination of active hydrogen.[9]

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Reported by R. P. Seven
November 7, 1947

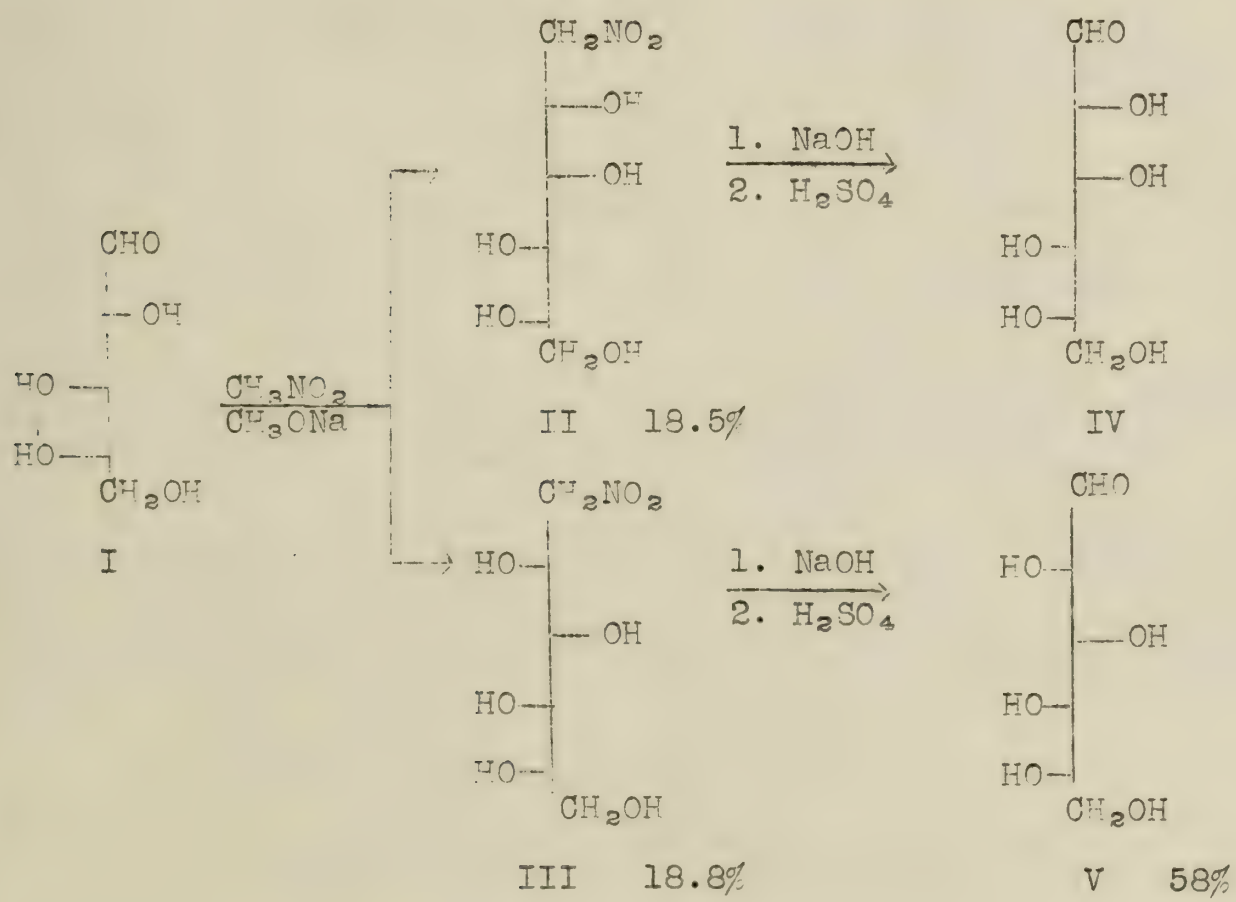
CARBOHYDRATE NITROALCOHOLS AND THEIR APPLICATION IN SUGAR CHEMISTRY

Recently Sowden and Fischer have prepared an interesting new type of sugar derivative, carbohydrate nitroalcohols, by the condensation of aldoses or their derivatives with nitromethane. These nitro compounds offer a new route in the synthesis of certain sugars and sugar derivatives. Some of the conversions in the carbohydrate series which have been effected through the nitroalcohol in termediate are illustrated below.

I. Lengthening of the Sugar Chain.

(a) Pentose to hexose.

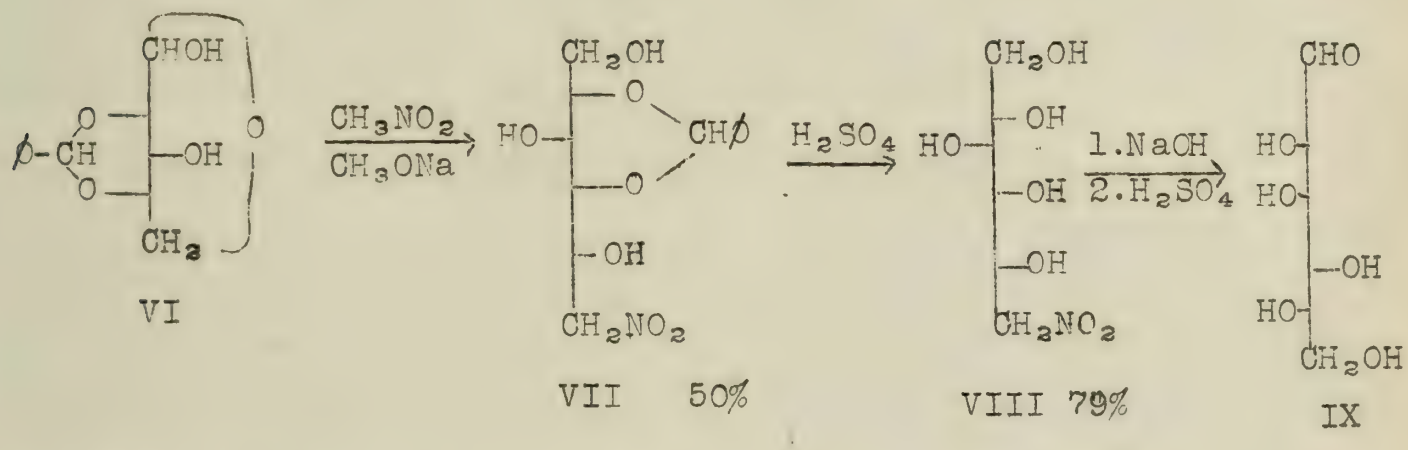
Condensation of L-arabinose (I) with nitromethane produced the two crystalline epimeric nitroalcohols, 1-nitro-1-desoxy-L-mannitol (II) and 1-nitro-1-desoxy-L-glucitol (III), which yielded, respectively, L-mannose (IV) and L-glucose (V) when their sodium salts were added to sulfuric acid (Nef reaction).



Similarly, D-glucose and D-mannose may be obtained from D-arabinose.

Unlike the addition of hydrocyanic acid to the arabinoses, which gives mainly the mannonic acid lactones, the addition of nitromethane seems to give the nitroalcohols with the glucose and mannose configurations in nearly equal amounts. This method is preferable to the cyanohydrin synthesis in that the operations are simpler, require much less time, and give yields which equal or better those obtained by the other method. The new synthesis is particularly advantageous in the preparation of the comparatively rare sugar, L-glucose, which is obtained in small yield from a long and tedious cyanohydrin synthesis. The method also may be attractive in preparing D-glucose containing isotopic carbon in the aldehyde group for biological study.

The new procedure affords a convenient source of L-gulose (IX) from 2,4-benzylidene L-xylopyranose (VI) which is obtained in good yield from 2,4-benzylidene sorbitol by cleavage with lead tetra-acetate.

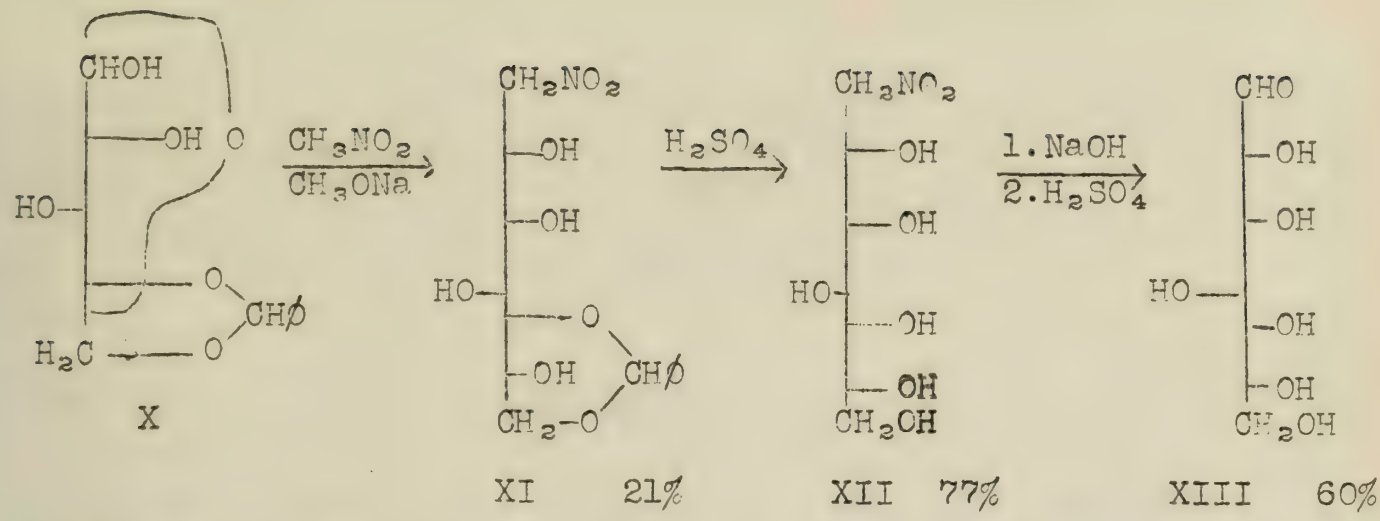


The 2,4-benzylidene 6-nitro-6-desoxy-D-sorbitol (VII) was apparently obtained pure, and none of the epimeric L-iditol derivative, whose concurrent formation may be expected, was isolated.

The only method previously recorded for the prepration of L-gulose involves the laborious and costly series of successive reductions with sodium amalgam: D-saccharic acid → D-glucuronic acid → L-gulonolactone → L-gulose. The yield of L-gulonolactone amounted to 15%, while the over-all yield in the steps illustrated above is about 25%.

(b) Hexose to heptose.

By means of the nitromethane condensation the C_7 sugar D-α-glucoheptose (XIII) has been prepared from 4, 6-benzylidene glucose (X).



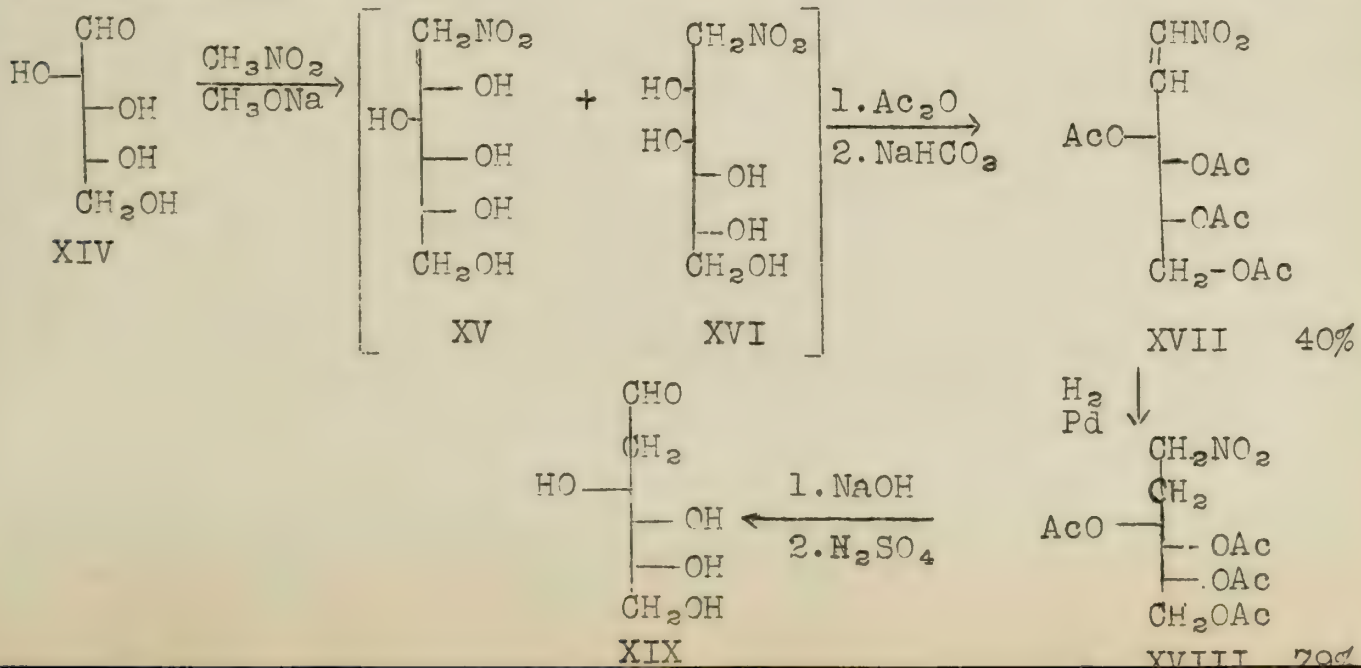
As in the case of nitroalcohol VII, the C_7 carbohydrate nitroalcohol was apparently obtained as a pure isomer; the epimeric D-β-glucoheptitol derivative was not isolated.

Although the conversion of the nitro derivative (XI) to D-α-glucoheptose (XIII) is quite satisfactory, the method is not attractive as a source of this C_7 aldose because of the low yields obtained in preparing benzylidene glucose from glucose and in the condensation of the former with nitromethane.

II. 2-Desoxy Sugars from Carbohydrate Nitroölefins

Nitroölefins have been prepared from the carbohydrate nitroalcohols by a reaction discovered by Schmidt and Rutz in which α-acetoxy primary nitroparaffins, when treated in ether solutions with bicarbonate, readily lose one mole of acetic acid to yield the corresponding olefin. 2-Desoxy sugars may be obtained from these carbohydrate nitroölegins by catalytic hydrogenation of the double bond and hydrolysis of the resulting 1,2-didesoxynitroalcohol.

D-arabo-2-desoxyhexose (XIX) has been prepared in this manner from D-arabinose (XIV).



Carbohydrate nitroölefins were obtained from D-xylose, L-xylose, D-ribose, and D-arabinose in yields of 20-40%; D-glucose, however, yielded only 5% of the corresponding C_7 nitroölegin. This method of producing 2-desoxy sugars should prove of value as a supplement to previous methods based on the hydration of glycals and on the reductive cleavage of thioethers.

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Reported by Charles L. Zirkle
November 7, 1947

CATALYTIC HYDROGENATION OF SULFUR-CONTAINING COMPOUNDS

I. Introduction.--Recent work on the hydrogenation of sulfur-containing compounds has been patented by the E. I. duPont de Nemours and Company.

II. Catalysts (5).--A recently patented invention provides a new hydrogenation catalyst that is relatively inexpensive, highly active, poison resistant, and noncorroding. It provides a process for the manufacture of the catalyst and gives a more effective method for catalytic hydrogenation. One of these catalysts is prepared by alloying cobalt and aluminum. This alloy is ground to a fine powder, treated with boiling H_2O and $Na_2S.9H_2O$, boiled, and allowed to settle. The resultant sludge is treated with $Na_2S.9H_2O$, NaOH, boiled again, allowed to settle, and washed, yielding a thick aqueous paste catalyst. Another widely used type catalyst is prepared by treating $CoCl_2.6H_2O$ with $Na_2S.9H_2O$, S, and H_2O. This product is washed, then hydrogenated in an electric furnace, yielding the reduced catalyst. It must be protected from air as it is pyrophoric.

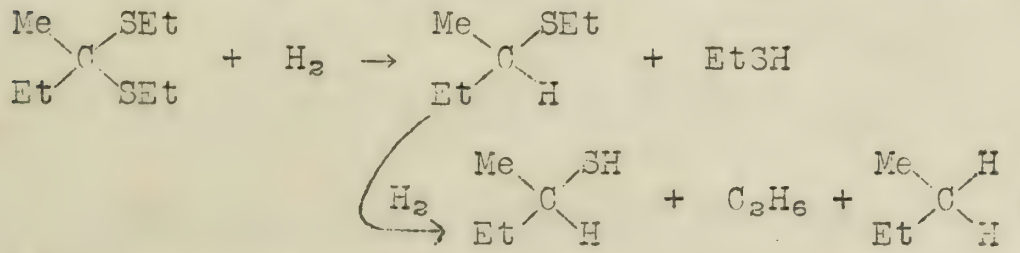
III. General.--The following reactions shown are representative of the hydrogenation of the particular type compounds. The conditions of the various reactions vary with the substances being reduced. Temperatures will generally vary from 125° to 250°C with pressures ranging from 1000 to 3000 pounds per square inch. In all cases one of the above mentioned type catalysts is used.

IV. Aliphatic Thiols (3).--This invention describes an economical catalytic method for the process of converting aliphatic sulfides to aliphatic thiols.

Examples:

$$(\underline{n})\text{-}C_4H_9\text{-}S\text{-}S\text{-}(\underline{n})\text{-}C_4H_9 + H_2 \rightarrow CH_3(CH_2)_3SH \qquad (73\%) \qquad (1)$$

$$(\underline{n})\text{-}C_4H_9\text{-}S\text{-}(\underline{n})\text{-}C_4H_9 + H_2 \rightarrow CH_3(CH_2)_3SH \qquad (67.5\%) \qquad (2)$$



(3)

$$\emptyset CH_2SSCH_2\emptyset + H_2 \rightarrow 2\ \emptyset CH_2SH \qquad (4)$$

$$\emptyset CH_2SH + H_2 \rightarrow \emptyset CH_3 + H_2S \qquad (5)$$

(5) is a side reaction of reaction (4). This side reaction is generally noted only in the production of aliphatic thiols which have an aryl group attached to the carbon atom bearing the thiol group.

$$(CH_2OH(CHOH)_4CH_2S)_2 + H_2 \rightarrow CH_2OH(CHOH)_4CH_2SH \qquad (6)$$

V. <u>Thiols from Esters of Thio Acids</u> (9).--

Examples:

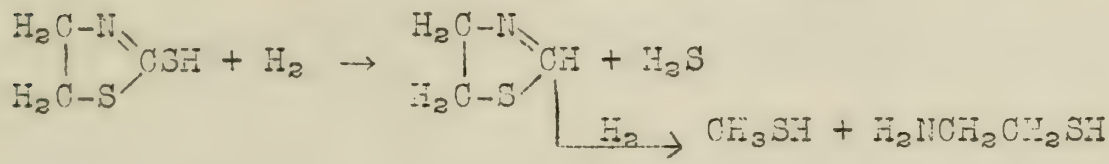
$$C_{12}H_{25}S\overset{O}{\underset{O}{\overset{\uparrow}{\underset{\downarrow}{S}}}}ONa + 4H_2 \rightarrow C_{12}H_{25}SH + NaOH + H_2S + H_2O \quad (82\%) \qquad (7)$$

$$C_{12}H_{25}SCN + H_2 \rightarrow C_{12}H_{25}SH + HCN \quad (80\%) \qquad (8)$$

$$C_4H_9O-\overset{S}{\overset{\uparrow}{C}}-SK + 2H_2 \rightarrow C_4H_9OCH_2SH + KSH + C_4H_9OH \qquad (9)$$

$$+ CH_3SH + CH_2S \text{ (Polymeric)}$$

$$C_4H_9O-\overset{S}{\overset{\uparrow}{C}}-SC_{12}H_{25} + H_2 \rightarrow C_4H_9OH + C_{12}H_{25}SH + CH_3SH \qquad (10)$$



(11)

VI. <u>Catalytic Hydrogenation of Aldehydes in Presence of H_2S</u> (4,19).--In this reaction it is usually more convenient to combine into a single operation the formation and hydrogenation of the aldehyde.

Examples:

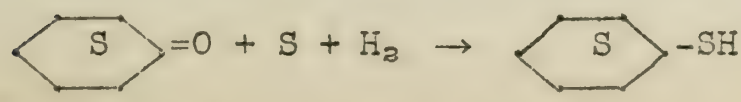
$$CH_3(CH_2)_5\overset{O}{\overset{\uparrow}{C}}-H + H_2S \rightarrow CH_3(CH_2)_5\overset{H}{\overset{\uparrow}{C}}=S + H_2O \qquad (12)$$

$$\xrightarrow{H_2} CH_3(CH_2)_5\overset{HH}{\overset{\downarrow}{C}}-SH$$

$$CH_3(CH_2)_5CHO + HS(CH_2)_3CH_3 \xrightarrow{H_2} CH_3(CH_2)_6S-(CH_2)_3CH_3 \qquad (13)$$

VII. <u>Catalytic Hydrogenation of Carbonyl Compounds in Presence of H_2S</u> (2).--

Examples:



(14)

$$\emptyset\text{-}CHO + S + H_2 \rightarrow \emptyset CH_2SH \qquad (15)$$

Under similar conditions, laurone, $(C_{11}H_{23})_2CO$, and palmitone, $(C_{15}H_{31})_2CO$ are converted into the corresponding thiols in excellent yields.

VIII. Lactones of Mercapto Carboxylic Acids and Process of Preparing Them (6).--

Examples: (The reactions taking place during the hydrogenation in a single operation may be formulated as follows).

$$CH_3CO(CH_2)_2COOH + H_2S \rightarrow CH_3\overset{S}{\overset{\|}{C}}(CH_2)_2COOH \underline{+ H_2}$$

$$CH_3\underbrace{CH(CH_2)_2C}_{S}=O \longleftarrow CH_3\overset{SH}{\overset{|}{C}H}(CH_2)_2COOH \qquad (16)$$

$$HOOC(CH_2)_2\overset{O}{\overset{\|}{C}}(CH_2)_2COOH + H_2S \rightarrow HOOC(CH_2)_2\overset{S}{\overset{\|}{C}}(CH_2)_2COOH \underline{H_2}$$

$$HOOC(CH_2)_2\underbrace{CH(CH_2)_2C}_{S}=O \longleftarrow HOOC(CH_2)_2\overset{SH}{\overset{|}{C}H}(CH_2)_2COOH \qquad (17)$$

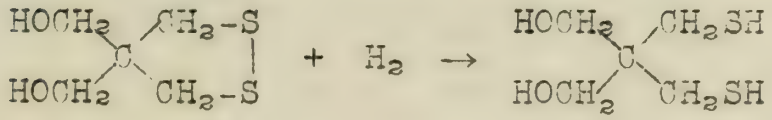
IX. Preparation of Hydroxy Thiols (7,11).--Catalytic hydrogenation of the thiocarbonyl compound is best accomplished in a single operation.

Examples:

$$\text{Dextrose} + H_2S \rightarrow CH_2OH(CHOH)_4\overset{H}{\overset{|}{C}}=S \xrightarrow{H_2} CH_2OH(CHOH)_4CH_2SH \qquad (18)$$

$$\text{Laevulose} + H_2S \rightarrow CH_2OH(CHOH)_3\overset{S}{\overset{\|}{C}}CH_2OH \xrightarrow{H_2} CH_2OH(CHOH)_3\overset{SH}{\overset{|}{C}}HCH_2OH \qquad (19)$$

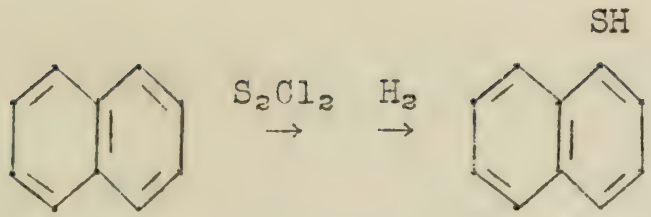
$$HOCH_2CH_2SSSCH_2CH_2OH + 2H_2 \rightarrow 2\ HOCH_2CH_2SH \qquad (20)$$



(21)

X. Preparation of Thionaphthols and Other Aromatic Thio Compounds (10,8,15).--

Examples:



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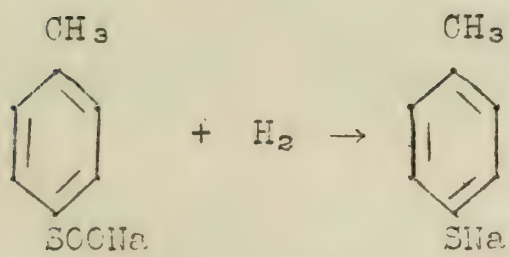

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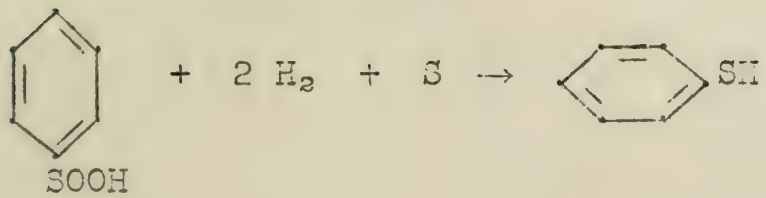

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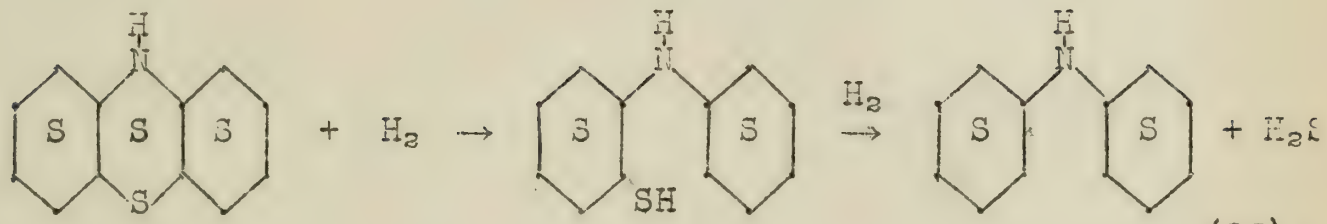

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(7) 2,402,640	(8) 2,402,641	(9) 2,402,642
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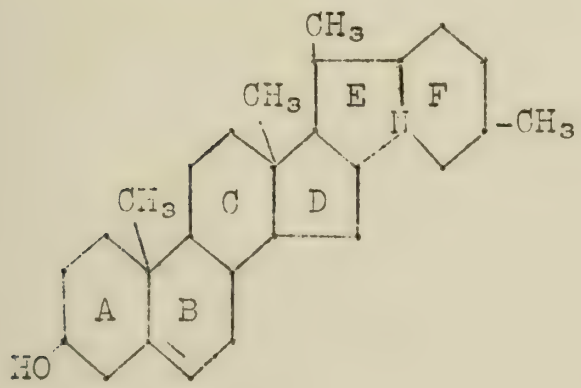
Reported by A. H. Anderegg
November 7, 1947

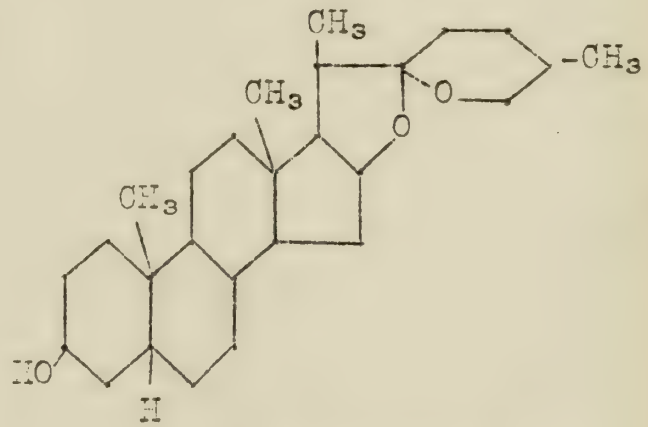
SOLANIDINE AND ITS RELATION TO THE VERATRINE ALKALOIDS

Solanidine, known since 1820, is of interest because of a recent partial synthesis proving its structure. It is found in the common potato plant (Solanum tuberosum) as the glucoalkaloid, solanine-t, as well as in other plants of the same species in similar combinations. Several cases of severe poisoning due to the ingestion of potatoes or potato plants containing an abnormally high content of solanine-t have been reported. It causes a drop in blood pressure, dilates the perpheral blood vessels and increases the body temperature.



Solanidine

I



Sorsasapogenin

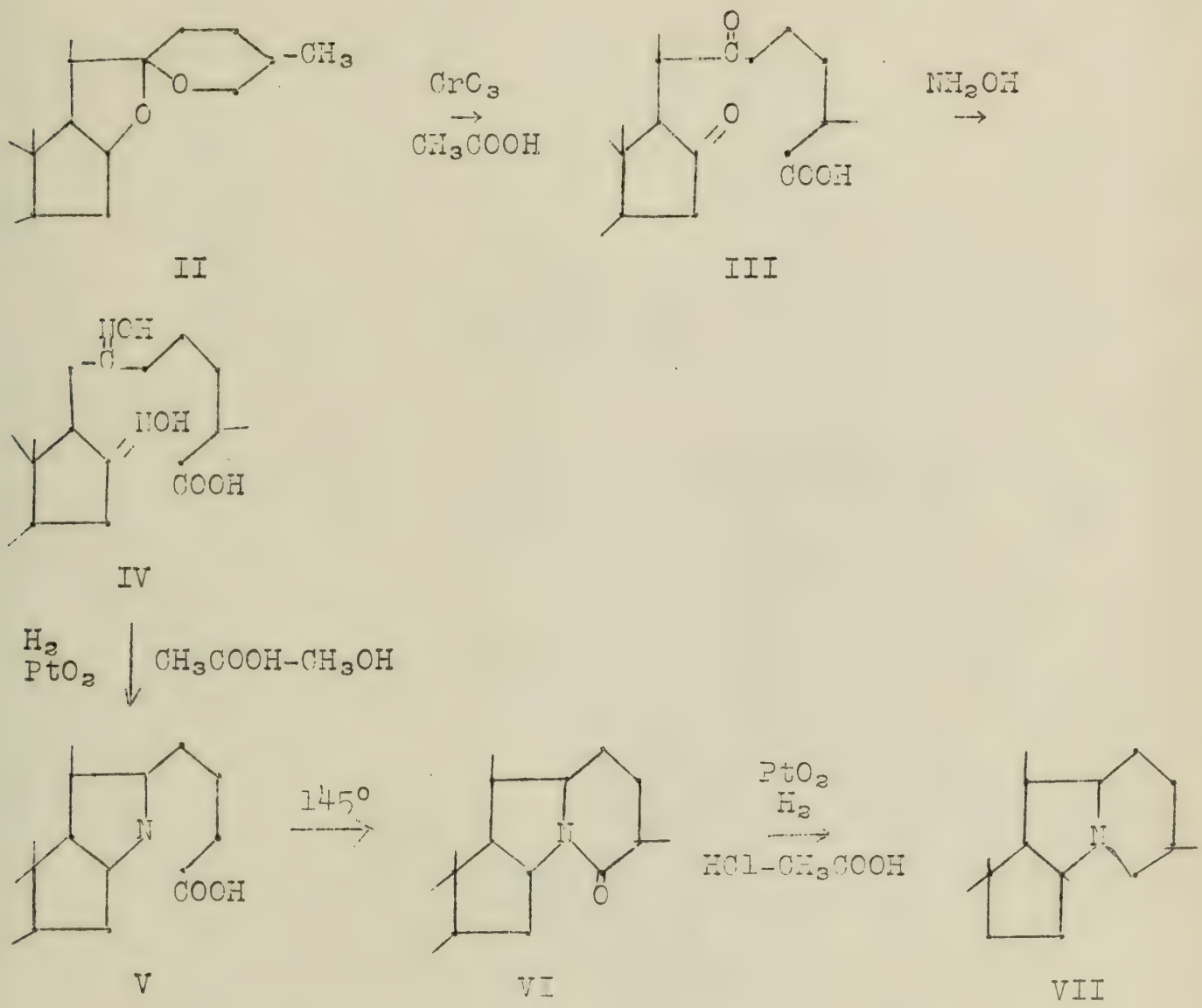
II

Oddo and Caronna have shown that the gluco-alkaloid has the structure solanidine-d glucose-d galactose-d rhamnose. Hydrolysis gives the alkamine, solanidine, which has the composition $C_{27}H_{43}ON$. It contains a double bond, a secondary hydroxyl group, a tertiary nitrogen to which no methyl groups are attached, and gives a digitonide. On dehydrogenation with selenium the Diels hydrocarbon which is characteristic of sterols is produced, as well as a basic fraction $C_8H_{11}N$, identified as 2-ethyl-5-methyl pyridine. From these data and from comparison of the infrared spectra of the alkaloid and the sterols, structure I was proposed.

However, since this was inferred entirely from degradation and transformation experiments, Jacobs and Uhle attempted a partial synthesis using a naturally occurring steroid, sarsasapogenin (II), as the starting material. This had the required iso-octyl side chain, and if the oxygens could be replaced by a nitrogen, a dihydrosolanidine would result. Prelog had already prepared and characterized the four sterioisomeric dihydrosolanidines with the cis and trans configurations of Rings A and B of both the 3α(OH) and the 3β(OH) series by hydrogenation of solanidine.

Oxidation of sarsasapogenin acetate with chromic oxide and acetic acid gave the diketo acid III which can then be converted

to the dioxime IV. Hydrogenation of IV with platinum oxide catalyst in a methanolic-acetic acid solution gave the secondary amine V which was changed to the lactam VI by heating at 145°. Reduction with an active PtO_2 catalyst in a HCl-methanol solution gave VII which was identified as the allosolanidanol (3β) of Prelog.



The Veratrine Alkaloids.--The alkaloids derived from the Veratrum species of plants are very similar to those of the Solanum species. They occur as two general types - the esters and the non-esters. Hydrolysis of the esters gives the free alkamine and one or more of the following acids: acetic, methyl ethyl acetic, methyl ethyl glycolic and tiglic. The non-esters consist of either the free alkamine or one attached in a glucosidic linkage with glucose. The veratrine alkaloids all exert a strong physicological effect on the respiratory and circulatory systems with the esters causing the greater response.

Alkamine	Molecular Formula	Double Bonds	Nature of Nitrogen	Se dehydrogenation Products	
				Basic	Neutral
Cevine	$C_{27}H_{43}O_8N$	1	3°	$C_8H_{11}N$	Fluorene type
Germine	$C_{27}H_{43}O_8N$	1 (?)	3°	$C_8H_{11}N$	Fluorene type
Protoverine	$C_{27}H_{43}O_9N$	1	3°	$C_8H_{11}N$	Fluorene
Jervine	$C_{27}H_{39}O_3N$	2 (?)	2°	$C_8H_{11}+C_8H_{11}ON$	Fluorene type
Rubijervine	$C_{27}H_{43}O_2N$	1	3°	$C_8H_{11}N$	Diels type
Isorubijervine	$C_{27}H_{43}O_2N$	1	3°	$C_8H_{11}N$	Fluorene type
Solanidine	$C_{27}H_{43}ON$	1	3°	$C_8H_{11}N$	Diels hydrocarbon
Solasodine	$C_{27}H_{43}O_2N$	1	3°	$C_8H_{11}N$	Diels hydrocarbon

Although there are many similarities with those of the solanidine alkaloids, the main difference appears in the products of selenium dehydrogenation. The presence of fluorene derivatives rather than those of phenanthrene suggest that the B ring may be five membered with a methyl group attached to carbon 5. While it might be possible that ring contraction could take place, such derivatives do not appear in the known sterols under the same conditions. If it is a five membered ring, the position of the double bond becomes uncertain also for it could not exist at the 5,6 position. The pyridine fraction suggest the same structures for rings E and F as in solanidine, although in jervine one hydroxy group probably appears on the F ring. All the oxygen atoms appear to be present as hydroxy groups, for active hydrogen determinations parallel the number of oxygen atoms present. The position of these groups has not been determined.

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Veratrine Alkaloids

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Reported by G. L. Shoemaker
November 14, 1947

ADDITION OF AROMATIC HYDROCARBONS TO THE CARBONYL GROUP

In attempting to prepare diphenyl diacetyl from symmetric dibrom diacetyl by a Friedel-Crafts reaction with benzene, M. Herzog (1), a pupil of Ruggli's, obtained a compound containing two bromine atoms (empirical formula, $C_{10}H_{10}O_2Br_2$) and corresponding to the addition of a molecule of benzene to the diacetyl. Structure analysis showed that instead of the expected Friedel-Crafts reaction, an addition of benzene to the carbonyl group had taken place. Further investigation showed that this reaction is quite general for adjacent diketones (2).

(1) $$BrCH_2\underset{O}{C}-\underset{O}{C}-CH_2Br + \phi\text{-}H \xrightarrow[\substack{75^\circ \\ 1\ \text{hour}}]{AlCl_3} BrCH_2-\underset{OH}{\overset{\phi}{C}}-\underset{O}{C}-CH_2Br$$

(2) $$CH_3-\underset{O}{C}-\underset{O}{C}-CH_3 + Ar\text{-}H \xrightarrow{AlCl_3} CH_3-\underset{OH}{\overset{Ar}{C}}-\underset{O}{C}-CH_3$$

Ar = ϕ-, CH_3-  -, CH_3-  -
CH_3

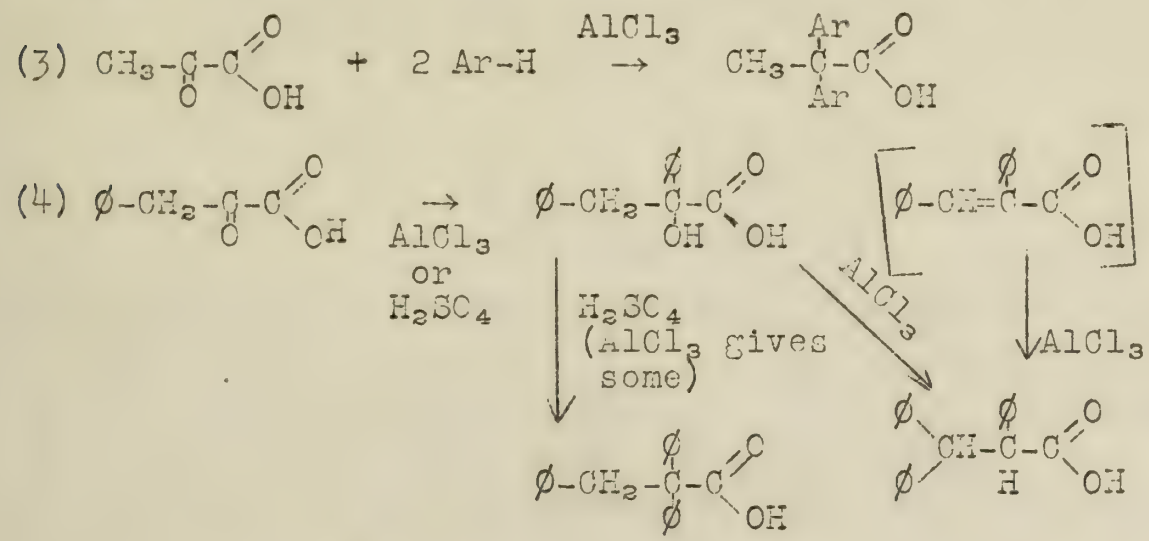
Since the bromine substituted diacetyl gave a better yield than diacetyl itself, the reactions of the tetra brom and hexabrom diacetyl were investigated. The yield for the di brom and tetra brom derivatives were about the same, but surprisingly the hexabrom diacetyl would not enter into this reaction. In no case could a second molecule of benzene be added by intensifying the conditions.

Dipropionyl and α,α'-dipropionyl did not add benzene in this reaction.

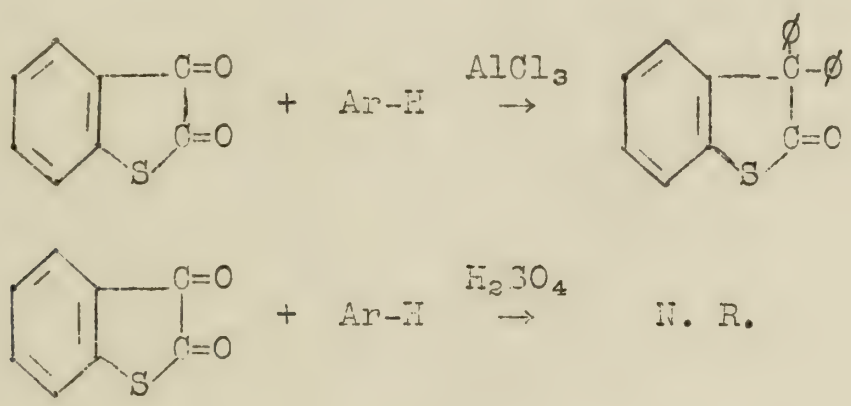
The only analogous $AlCl_3$ catalyzed additions of benzene to a carbonyl group were the addition of benzene to the aldehyde group of phenyl glyoxol, reported by Fuson (6), and the addition of benzene to the aldehyde group of chloral reported by Dinesman (7).

The H_2SO_4 (8,9,10) catalyzed addition of benzene to the carbonyl group of keto acids had previously been known. To find out if the above described reaction was analogous to this H_2SO_4 catalyzed addition, $AlCl_3$ was substituted for H_2SO_4 and the reactions described in the literature were repeated (4). In general it was discovered that the reactions proceed in the same manner and that the two catalysts are of approximately equal strength. Pyruvic acid will add two molecules of benzene under the influence of $AlCl_3$ and the intermediate, atrolactic acid, adds one benzene ring under these same conditions. The dibrom pyruvic acid will add only one hydrocarbon neucleus to form the dibrom atrolactic acid. The tri-

brom derivative gave no reaction. A difference in the addition products of phenyl pyruvic acid was observed with the two catalysts.



In these reactions an enol form is possible but the reaction of thio isatin, where enolization is impossible, shows that this mechanism is not essential.



A search of the literature revealed no addition to the carbonyl group of α-halogen ketones but instead that they reacted in the normal Friedel-Crafts manner (3).

In the above described reactions, an acid catalyzed addition of an aromatic ring to the carbonyl group is the first step. This may be followed by dehydration and addition of the aromatic compound to the double bond or by a normal Friedel-Crafts reaction on the resulting alcohol (reaction 4). The acid catalysts in order of decreasing strength are: $AlCl_3$ and H_2SO_4 > HCl > $ZnCl_2$ > glacial acetic acid. The aromatic components in order of reactivity are: 3° amines > phenols > phenol ethers > aromatic hydrocarbons (4).

<u>Conclusion</u>.--The carbonyl group can add an aromatic hydro-

carbon under the influence of an acid catalyst if activated by an adjacent carbonyl, carboxy, or nitrile group (5). In the above described systems, an adjacent phenyl substituted or tri halogen substituted methyl group deactivates the carbonyl group, while an adjacent mono or dihalogen substituted methyl group activates the carbonyl group.

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Reported by Hugh V. Anderson
November 14, 1947

RECENT DEVELOPMENTS IN THE IDENTIFICATION OF ORGANIC COMPOUNDS

The derivatives and tests outlined in this abstract are those likely to be the most general in application.

I. Carboxyl Compounds.--Buu-Hoï (1) has reported that the diamides of aliphatic monocarboxylic acids obtained from 1,5-naphthalenediamine or p-phenylenediamine are easily prepared, well-defined, crystalline substances of sharp melting points. Diamides of either series exhibit linear regularity of melting point over an ample range. It is especially in this regard that the new derivatives appear superior to those which have been used heretofore. Fifty-one (51) diamides are reported.

II. Hydroxyl Compounds, Amines, and Ethers.--p-Nitrophenylacetyl chloride has been proposed (2) as a reagent for the identification of alcohols, phenols, symmetrical ethers, and amines, the reactions involved being esterification and the preparation of amides. The ethers form the same esters as the corresponding alcohols, the presence of zinc chloride in the reaction mixture serving to cleave the ether. Although the esters from the lower aliphatic alcohols are liquids at room temperature, the phenolic esters and the amides are crystalline solids of sharp melting points in a moderate temperature range. Differentiation of melting points of the derivatives usually is good.

Renfrow and Chaney (3) have developed an exchange reaction (now used in this laboratory) between esters and 3,5-dinitrobenzoic acid as a means of identification, without isolation, of the alcohol component of the ester. The reaction is not applicable to esters that react readily with concentrated sulfuric acid or that have molecular weights over 250. Derivatives are listed for thirteen (13) alcohols from thirty-eight (38) esters.

Research has been conducted by Plattner and Geiger (4) on the use of the acid chloride of betaine hydrochloride, "betainyl dichloride", (I), in the preparation of water-soluble derivatives of alcohols and amines. Primary, secondary, and tertiary alcohols,

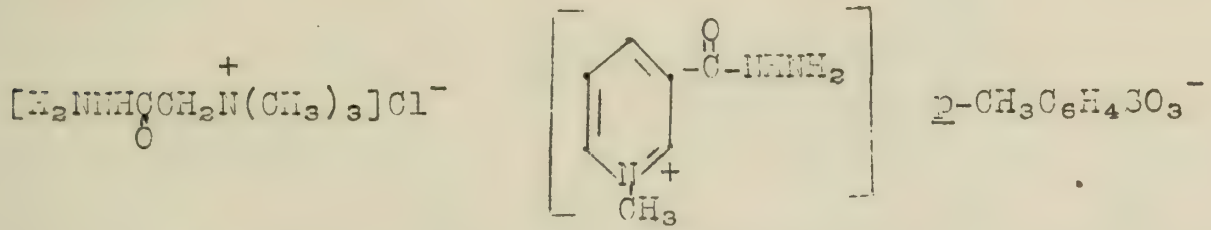
$$[(CH_3)_3N^+-CH_2C(=O)Cl]Cl^- + ROH \rightarrow$$

$$\text{I} \qquad [(CH_3)_3N^+-CH_2C(=O)OR]Cl^- + HCl$$

phenols, and primary and secondary amines react with "betainyl dichloride" in hot chloroform quickly and quantitatively to form the ester-(or amide-)hydrochloride. The unknown component may be

identified by the melting point of the derivative or by conversion of the ester (or amide) salt to a picrate. The latter course is suggested when the reaction product is hygroscopic or otherwise not obtainable in a sharply melting, crystalline form.

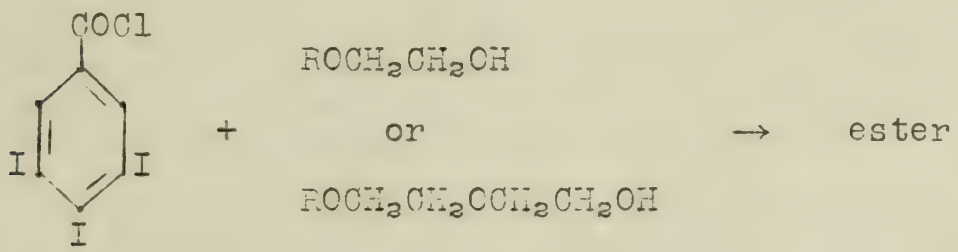
The use of this reagent is analogous to that of Girard's reagents (II) and N-methyl-β-carbohydrazidopyridinium p-toluenesulfonate (5) (III) for aldehydes and ketones. All three re-



II "T" III

agents convert organic compounds to water-soluble derivatives from which the original compounds may be recovered in pure form. The authors have characterized nine (9) alcohols and phenols and two (2) amines.

O'Donnell and Carey (6) have shown 3,4,5-triiodobenzoyl chloride to be useful in the preparation of solid esters of cellosolves and carbitols, organic compounds previously difficult to characterize. The triiodobenzoates of the nine (9) cellosolves

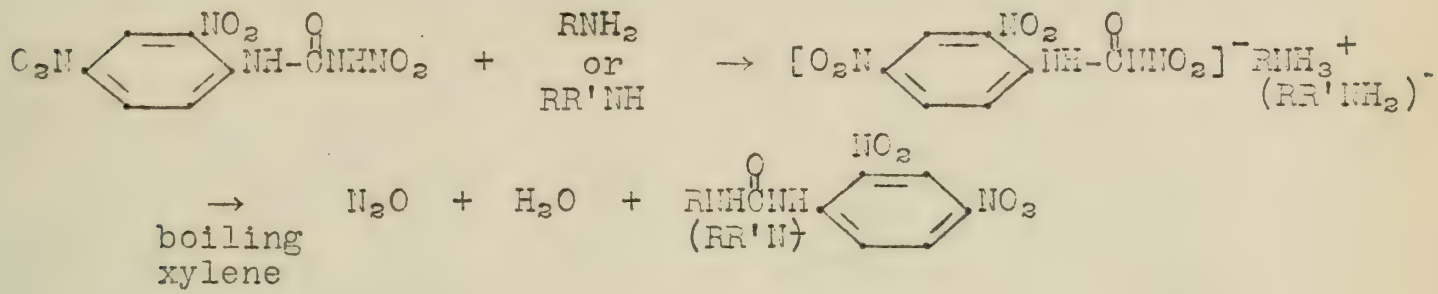


and carbitols examined are easily prepared, crystalline solids with melting points ranging from 53° to 153°C.

Heinrich and Schuler (7) have suggested the color reactions with stabilized diazonium salts as a means of identifying dihydroxybenzene derivatives. Stable and distinct colors in acid and basic media are reported for the reactions between phenol, catechol, resorcinol, hydroquinone (and tyrosine and tyramine) and the α- and β-naphthalene sulfonic acid salts of various substituted diazobenzenes.

N-nitro-N'-2,4-dinitrophenylurea has been investigated by McVeigh and Rose (8) as a reagent for the preparation of derivatives of primary and secondary amines. The reagent acts as a

moderately strong acid and forms stable salts with the amines. These salts are insoluble in hydrocarbon solvents and decompose in boiling xylene to form second derivatives, N,N'-disubstituted ureas. The reagent is prepared by the direct nitration of N-2,4-



dinitrophenylurea. The authors have described four (4) amine salts and twenty-one (21) substituted ureas.

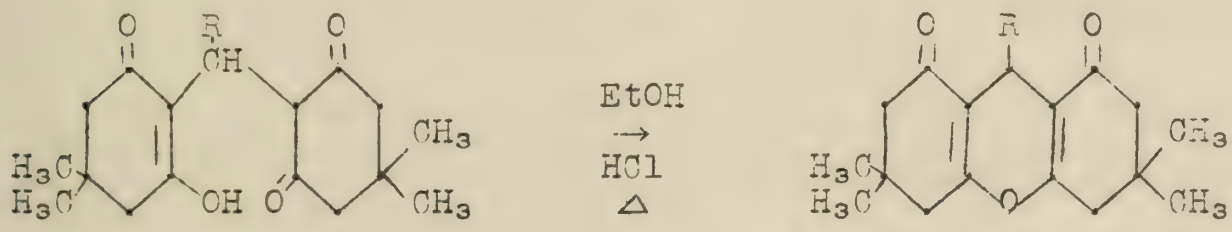
III. Carbonyl Compounds.--The action of sodium nitroprusside, $Na_2Fe(CN)_5NO$, in the identification of aldehydes and ketones and other bisulfite-binding compounds is described by Jonnard (9). The test involves the formation of the bisulfite addition product, the destruction of excess HSO_3^- by NaCN, and the production of the color on addition of the nitroprusside. The reaction is reported to be more conclusive and of greater scope than other similar tests, and is also valid for sterols, certain indole derivatives, and thiols. Colors are reported for sixty-seven (67) compounds.

Determination of the presence of aldehydes in concentrations of 1:100,000 is possible through a color reaction with diazotized sulfanilic acid, according to the work of Mossini (10). Colors are reported for various aldehydes and ketones, imidazole derivatives, reducing sugars, sucrose, and starch.

Twenty-three (23) aldehydes and ketones have been characterized by McVeigh and Rose (11) through the preparation of 2,4-dinitrophenylsemicarbazones. The derivatives have high, sharp melting points and are insoluble in water and only sparingly soluble in organic solvents. These solubility characteristics suggest an advantage in ease of preparation and purification over the unsubstituted semicarbazones. Like the latter, the new derivatives can be hydrolyzed to generate the carbonyl compound.

Oxydimorphine appears to be a specific reagent for the aldehyde function, in work reported by Breton (12). Distinct, individual colors are given by acyclic, cyclic, aromatic, and heterocyclic aldehydes with this reagent in concentrated sulfuric acid. Colors are listed for thirteen (13) aldehydes. The test is also valid for reducing sugars and those easily hydrolyzed in the reaction mixture to sugars with free-$C\overset{O}{\underset{H}{}}$ groups.

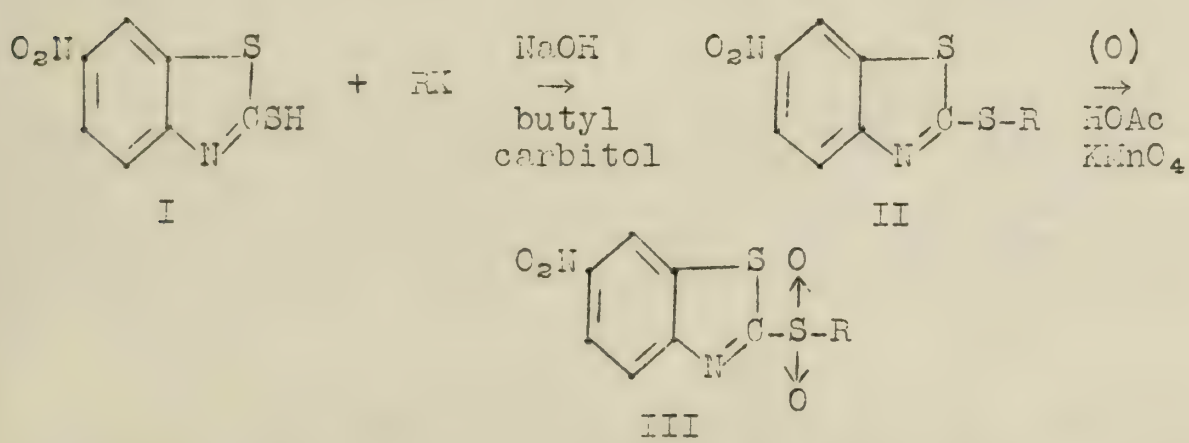
An extension of the well-known use of methone as a derivative for aldehydes has been reported by Horning and Horning (13). The methone derivatives (I) can be cyclized (in the case of aromatic and saturated aliphatic aldehydes) to an octahydroxanthene (II) by refluxing in 80% EtOH with HCl as a catalyst. The new compound is a colorless, crystalline solid of sharp melting point. Derivatives for forty (40) aldehydes are listed. The reaction is now



I II

used in this laboratory.

IV. Alkyl Halides.--Primary and secondary alkyl and cycloalkyl halides, usually somewhat more difficult to identify than other organic compounds, can be easily characterized by the reaction with 6-nitro-2-mercaptobenzothiazole (I), according to Cutter and Golden (14). The reagent yields two derivatives - the 6-nitrobenzothiazole alkyl sulfides (II) and the corresponding sulfones (III).



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The reagent is prepared by the nitration of benzothiazole disulfide, "Altax", a commercially available vulcanization accelerator, and the reduction of the dinitrodisulfide to 6-nitro-2-mercaptobenzothiazole, known as "Nitro Captax". The reagent works equally well with iodides, bromides, and chlorides. For the last-named, however, equimolar amounts of potassium iodide are added to the reaction mixture. The sulfide derivatives are rather low-melting (60-120°C), so that oxidation to the sulfone is generally recommended. Melting points are listed for fourteen (14) alkyl groups.

V. Hydrocarbons.--2,4,7-trinitrofluorenone has been reported by Orchin and Woolfolk (15) and by Orchin, Reggel, and Woolfolk (16) as a reagent for the formation of equimolar (in most cases) molecular complexes with aromatic polynuclear hydrocarbons. The trinitrofluorenone (TNF) is superior to picric acid in that the reagent is not as soluble in water as the latter. The reaction of complex formation with TNF is thus not as prone as that with picric acid to hydrocarbon precipitation before complex formation and hydrocarbon precipitation in excess on the complex, making analyses inaccurate.

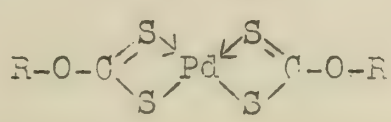
The new complexes are stable, crystalline, and highly colored, and melt sharply without decomposition. They can also be used for purification, the TNF being eliminated chromatographically or by reduction and acid extraction.

Adaveeshiah and Subba Jois (17) have reported the use of 4,6-dibromo-1,3-dinitrobenzene in the preparation of identifiable molecular complexes with aromatic polynuclear hydrocarbons, amines, and phenols. The complexes form in 1:1 and 1:2 (reagent:compound) molar ratios, and have sharp melting points. With naphthylamines, heating of the complex in EtOH yields second derivatives, N(2,4-dinitro-5-bromophenyl)-naphthylamines, likewise identified by their melting points.

VI. Carbohydrates.--A qualitative test for the determination of carbohydrate materials has been described by Dreywood (18). Anthrone in concentrated sulfuric acid produces a green coloration with carbohydrates and their derivatives. Terpenes, alkaloids, proteins, and simpler organic compounds do not interfere.

VII. Nitro Compounds.--Canbäck (19) has reported a series of color tests for nitro compounds with CH_3OK in CH_3OH. Mononitro compounds give no color, dinitro compounds yield blue or purple, and trinitro compounds, red. Results are described for fourteen (14) nitro compounds and fifty-nine (59) compounds nitrated as part of the test. $-NH_2$, -OH, and -COCH interfere with the color or inhibit the nitration.

VIII. Xanthates.--Palladium derivatives are reported by Bulmer and Mann (20) as a means of identifying CS_2 and many alkali xanthates. The alkyl palladium xanthates are non-ionic compounds with characteristic melting points exhibiting linear regularity.



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Reported by Herbert S. Elins
November 14, 1947

MEERWEIN REACTION AND APPLICATIONS

General.--In 1939, Meerwein and coworkers (10) found that diazonium compounds couple to activated unsaturated compounds in a slightly acidic medium. The coupling occurs in either the α-, β- or γ-position and forms different products depending on the functional group in the unsaturated compound. The conditions necessary for the reaction are: 1. aqueous-acetone solution; 2. the salt of a weak acid, ex: NaOAc; 3. cupric salt. The cold diazonium chloride solution, prepared from the amine, is added to the aqueous-acetone solution containing NaOAc, cupric salt, and the unsaturated carbonyl compound; and the temperature is raised to about 20° when the evolution of nitrogen begins.

$$ArN_2Cl + RCH{=}CHCO_2Et \rightarrow RCH{=}\underset{Ar}{C}{-}CO_2Et + N_2\uparrow + HCl$$

Effect of Substituents in Diazonium Compound.--For the same substituent in the o-, m-, p-positions, the yield of coupled product increases in the order o- < m- < p- (See Table I). The para-substituent gives the highest yield; the ortho- either gives a product difficult to purify or none at all. Negative substituents, NO_2-, COOH-, Cl-, SO_3H-, COOMe-, and COOEt-, give the highest yield of product, varying between 40 and 78% for the p-substituted diazonium chlorides.

Disubstituted diazonium chlorides, with one substituent in the ortho-position, give larger yields than the ortho-derivative itself (See Table II).

Naphthalene diazonium chlorides show similar steric effects; α- gives less yield than β-, and a second substituent in the α-derivative increases the yield (See Table III).

Effect of Unsaturated Compounds in Coupling.--α-β-unsaturated acids, esters, and nitriles, including acetylene derivatives, couple with diazonium compounds in the Meerwein reaction. But the resulting products differ.

1. Unsaturated acids that couple in α-position lose CO_2.

$$ArN_2Cl + C_6H_5CH{=}CHCO_2H \rightarrow C_6H_5CH{=}CHAr + N_2 + CO_2 + HCl$$

2. Unsaturated acids that couple in β-position retain CO_2 and acquire halogen.

$$ArN_2Cl + CH_3CH{=}CHCO_2H \rightarrow CH_3\underset{Ar}{C}H{-}\underset{Cl}{C}H{-}CO_2H + N_2$$

3. Unsaturated esters generally replace the H in α-coupling.

$$ArN_2Cl + C_6H_5CH{=}CHCH{=}CHCO_2Me \rightarrow C_6H_5CH{=}CHCH{=}\underset{Ar}{C}{-}CO_2Me + N_2 + HCl$$

4. Most unsaturated nitriles and some esters form the HX addition product.

$$ArN_2Cl + C_6H_5CH{=}CHCO_2Me \rightarrow C_6H_5\underset{Cl}{C}H{-}\underset{Ar}{C}H{-}CO_2Me + N_2$$

Not only α-coupling, as Meerwein indicated, but β- and γ-coupling also can occur. This is due to the aryl free radical attacking the C-atom in the unsaturated molecule, which is least sterically hindered.

TABLE I

Effect of o-, m-, p-Substituents

Diazonium Chloride	Unsat. Compd.	o-%	m-%	p-%
nitrobenzene	coumarin	11(10)	--	49.9(10)
toluene	cinnamic acid	12(2)	14(2)	48.8(10),40(2)
chlorobenzene	cinnamic acid	8(2),9(5)	16(5)	68.8(10),40(5)
nitrobenzene	cinnamic acid	43.9(10)	33(2)	58.4(10)
bromobenzene	cinnamic acid	8(5)	17(5)	23(5)
anisole	cinnamic acid	imp.(2)	--	49.2(10)
chlorobenzene	p-methoxy cinnamic acid	8,14(2)	--	61.2(10)
nitrobenzene	acrylonitrile	---	38(8)	48(8)
chlorobenzene	cinnamal-acetic acid	10(5)	29(5)	33(5)
nitrobenzene	cinnamal-acetic acid	10(1)	--	25(3)
diphenyl	cinnamal-acetic acid	0(4)	--	20(4)

TABLE II

Effect of Second Substitution on ortho-Substitution

Diazonium Chloride	Unsat. Compd.	Yd.% (Ref.)
2-chlorobenzene	cinnamic acid	9(5),8(2)
2,6-dichlorobenzene	cinnamic acid	0(2)
2,4-dichlorobenzene	cinnamic acid	34.4(10),26(2)

TABLE II CONTD.

Diazonium Chloride	Unsat. Compd.	Yd.%, (Ref.)
2,4-dichlorobenzene	methyl cinnamate	22.4(10)
2,5-dichlorobenzene	cinnamic acid	28(2)
2-chloro-5-methylbenzene	cinnamic acid	27(2)
2-nitro-4-methoxybenzene	cinnamic acid	18(2)
2-methoxy-5-bromobenzene	cinnamic acid	28(2)

TABLE III

Comparison of Naphthalene Compounds

Diazonium Chloride	Unsat. Compd.	Yield % (Ref.)
α-naphthalene	cinnamic acid	traces (2)
β-naphthalene	cinnamic acid	5(2)
4-nitro-1-naphthalene	cinnamic acid	12(3)

NOTE: The numbers in parenthesis are references.

α-coupling.--This is best known because cinnamic and cinnamalacetic acid derivatives are usually used in the reaction.

$$Ar_2NCl + C_6H_5CH{=}CHCH{=}CHCO_2H \rightarrow C_6H_5CH{=}CHCH{=}CHAr + N_2 + CO_2 + HCl$$

β-coupling.--Koelsch (8) found that acrylic and crotonic acid derivatives, which are less hindered at the β-position, couple there.

$$ArN_2Cl + CH_2{=}CHCN \rightarrow ArCH_2{-}CHCl{-}CN + N_2$$

γ-coupling.--Vinylacetic acid (2) couples in the γ-position in 5% yield.

$$p\text{-}Cl\_C_6H_4{-}N_2Cl + CH_2{=}CHCH_2CO_2H \rightarrow Cl{-}C_6H_4{-}CH{=}CHCH_2CO_2H + N_2 + HCl$$

Side Reactions.--The yields for the Meerwein reaction are low because of the variety of side reactions that interfere.

1. ArX forms through a normal Sandmeyer reaction; the stability of the diazonium compound is important because the reaction mixture reaches at least 20° before coupling occurs.

2. Unknown tars and diazo resins form.

3. Acetone reacts with the ArN_2Cl to form CH_3COCH_2Cl.

Excess diazo compound increases the yield slightly.

Mechanism.--First, Meerwein thought that ArN_2^+ formed an aryl cation, Ar^+, which combined to form an intermediate, which would either lose CO_2 or a proton or would unite with the X^- ion. Then this was shown to be wrong by Koelsch who found that β-coupling occurs and that steric factors were more important than the direction of polarization. Koelsch and Boekelheide (9) postulated that acrylic acid combines with the free radical, Ar·, at the β-C in order that the odd electron on the α-C could resonate into the neighboring >C=O group, while cinnamic acid adds the Ar· at the α-C so that the odd electron on the β-C is stabilized by resonance into the β-phenyl ring.

The diazo compound cannot itself form a free radical, but does so through the intermediate formation of the diazo acetate, which then adds to the unsaturated compound.

$$ArN_2^+ + AcO^- \rightleftarrows ArN{=}NOAc \rightarrow Ar\cdot + N_2 + AcO\cdot$$

$$Ar\cdot + RCH{=}CHR' \rightarrow ArCHR{-}C\cdot HR'$$

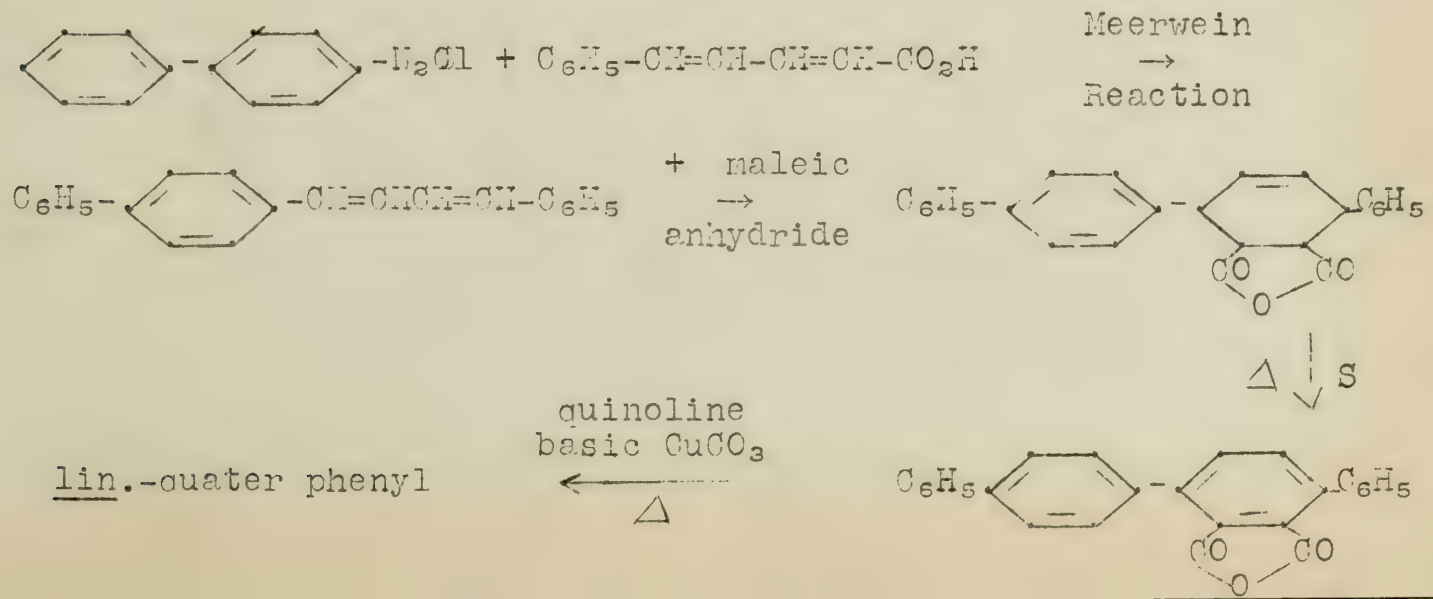
The postulated function of the Cu^{++} salt is:

$$ArCHR{-}C\cdot HR' + Cu^{++} \rightarrow Cu^+ + ArCHR{-}\overset{+}{C}HR'$$

$$Cu^+ + AcO\cdot \rightarrow Cu^{++} + AcO^-$$

But Bergmann and Schapiro (2) believe the reaction is ionic because the addition of Ar to vinylacetic acid does not follow the free radical, peroxide-catalyzed, addition of HBr, but the ionic HBr addition.

Applications.--Substituted cinnamic acid derivatives can be prepared by the Meerwein reaction, and then can be converted to unsymmetrical stilbenes, which can be reduced to unsymmetrical bibenzyls. Diphenyl butadienes of the trans, trans form can be prepared by this method. And the reaction can be utilized for a new synthesis of lin.-quater-phenyl (4).



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Reported by Bernard R. Bluestein
November 14, 1947

SOME ASPECTS OF INFRARED ABSORPTION SPECTROSCOPY

The measurement of infrared absorption spectra is possible because the frequencies of the vibrations of the atoms within a molecule coincide with the frequencies of infrared radiation. Many of these vibrations are "infrared active" (involve a change in dipole moment) and absorb all or part of incident radiation of the same frequency. The usefulness of this method depends upon two things: 1. The bond positions are very sensitive to structural changes, and 2. At least a few of the bands in a given spectrum can be ascribed to specific groups within the molecule. A more general statement is simply that the infrared spectrum of a molecule is probably the most distinctive characteristic of that material.

Instruments and Techniques.--The discussion which follows will be confined, for practical reasons, to the portion of the infrared region lying between 4000 cm^{-1} (2.5μ) and 667 cm^{-1} (15μ). The units used to locate points in this region are the micron, μ (1μ = 10,000 Å = 10^{-4} cm.) and the wave number, cm^{-1} [1 cm^{-1} = 1/λ (cm.)]. The instrument used in measuring these spectra is known as an infrared spectrometer, and consists essentially of the following parts: 1. a light source, 2. a dispersing means to spread out the radiation from the source so that narrow bands of light of known frequency can be selected, 3. a sample holder, and 4. a detector and amplifier system to measure the intensity of the radiation.

Samples can be studied as vapors, liquids, solutions, or solids. The desired amount of absorption is obtained by regulating the quantity of material in the light path. Small samples are usually sufficient; 0.1 cc. of a liquid and 3 to 10 milligrams of a solid.

Application.--In general the applications of infrared spectroscopy which are of interest to the organic chemist are as follows: 1. identification of organic compounds, 2. detection and identification of small amounts of impurities in organic compounds, 3. accurate quantitative determinations of the impurities, 4. a study of reaction mechanisms, speeds, and detection of intermediates, 5. study of isomerism and tautomerism, 6. study of association, 7. study of polymerization and copolymerization in the field of plastics, and 8. determination of geometrical structures.

Evaluation of the Infrared Method.--Ultraviolet absorption spectroscopy is at present more widely used as an aid to chemical research than is the infrared method. Ultraviolet spectra are well suited to the determination of conjugation ranging from diolefins through conjugated carbonyl compounds to aromatic hydrocarbons of lower molecular weights. The ultraviolet spectra of the higher molecular weight aromatics (9 carbons or more) become similar, and accurate analyses are often difficult if not impossible. The ultraviolet method is especially useful for the quantitative determination of a few aromatics (a maximum of perhaps four absorbing components in a single sample) in a mixture of other

hydrocarbons; it is not usually sensitive to simple olefins, paraffins, or naphthenes.

Infrared spectroscopy, on the other hand, is suited, to a somewhat lesser degree, for the determination of conjugation, and in addition can be used for the determination of paraffins, simple olefins, and naphthenes. Infrared is conveniently used in analyzing for 4 to 6 components, and has been used in the analysis of a few samples containing as many as 9 components. The greatest advantage of infrared spectroscopy depends upon the fact that it gives specific information as to the nature of the groups within the molecule. In addition every molecule gives a different spectrum.

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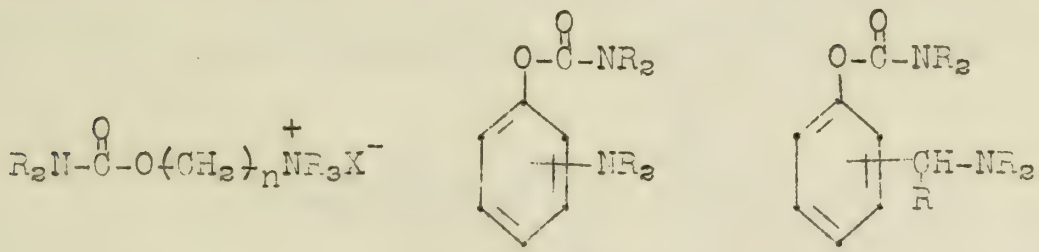
Reported by J. L. Johnson
November 14, 1947

SOME RECENT STUDIES ON THE RELATIONSHIP BETWEEN CHEMICAL CONSTITUTION AND TOXICITY

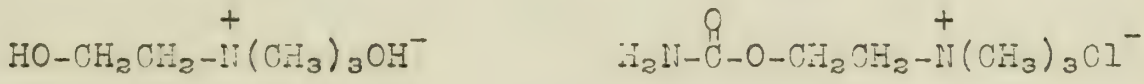
Haworth (1,2,3) has recently begun a new and systematic investigation of the influence of chemical constitution on physiolical activity, using types of compounds which had been studied to a great extent in the past. The first three types with which he has worked are I, II and III, in which R may be hydrogen, alkyl,



I II III

or aryl.

Compounds of type I are derivatives of the physiologically important base, choline. The powerful parasympathomimetic activity of acetylcholine has long been known, having first been extensively studied by Hunt and Taveau (4), and other similar types, such as "Doryl" (6) are even more active. The activity of these

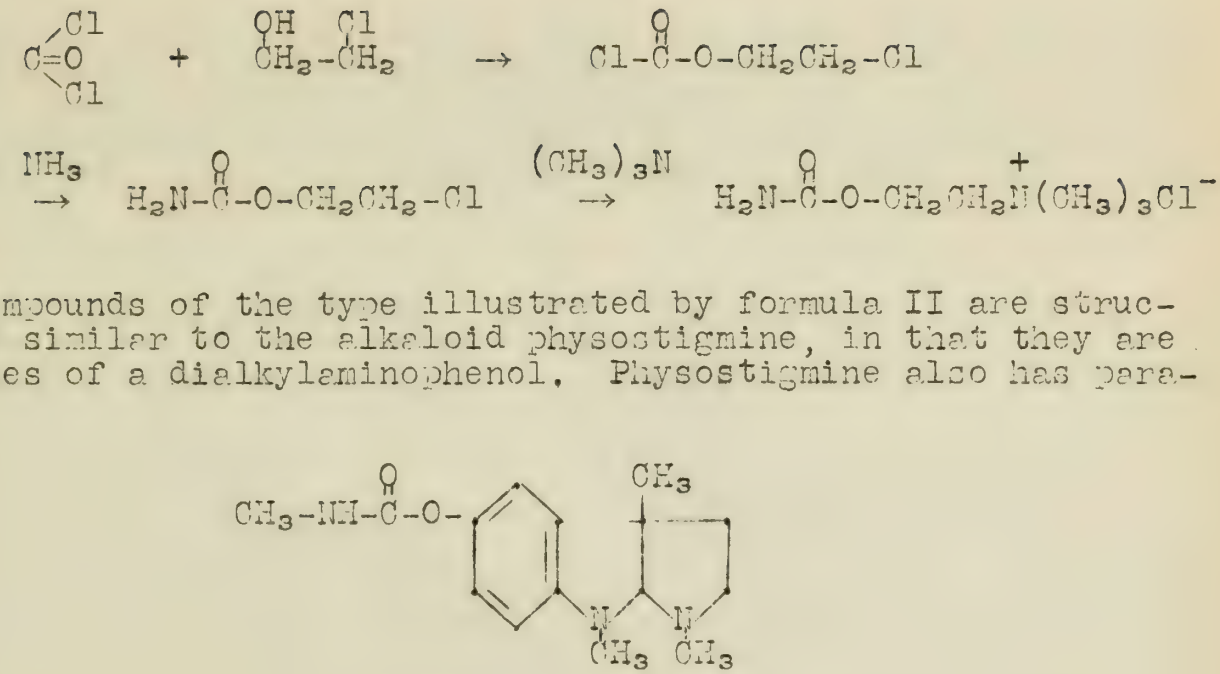


Choline "Doryl"

substances can be varied by altering the groups on the quaternary nitrogen, and by increasing the number of $-CH_2-$ groups (6). Stedman and his coworkers (1) prepared a great number of derivatives and homologues of type I, in which the alkyl groups on the urethane nitrogen atom were H, methyl, ethyl, propyl, allyl, phenyl and benzyl, X was Cl or I, and n varied from two to ten. They found that the toxicity of these substances was diminished by:

1. Replacement of one or both of the amide hydrogen atoms by alkyl groups.
2. Increasing the number of $-CH_2-$ groups.
3. Removal of the urethane grouping, or replacement of it by another group, such as the vinyl ether group.

The general preparation method used for these compounds is illustrated by the following synthesis of Doryl.



Compounds of the type illustrated by formula II are structurally similar to the alkaloid physostigmine, in that they are urethanes of a dialkylaminophenol. Physostigmine also has para-

Physostigmine

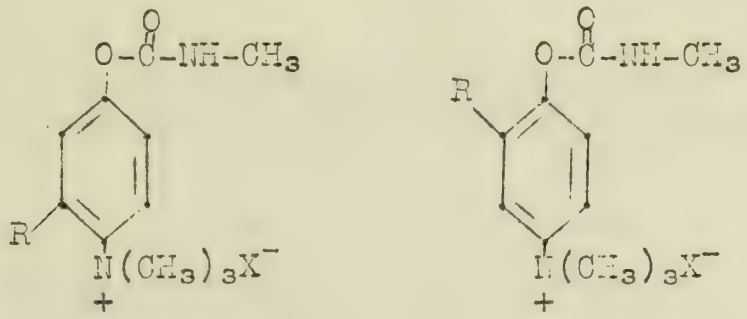
sympathomimetic activity, and produces miosis, or contraction of the pupils, when a solution of it is applied to the eyes. Stedman (7,9) synthesized and investigated the miotic acitivity of a number of compounds of type II, and concluded that those which are esters of methylcarbamic acid are the most active. Aeschlimann and Reinert (10) extended the work and confirmed Stedman's findings. Stedman found the general activity of the tertiary amines was in the order o- > m-, p-, but that on conversion to the corresponding quaternary salts the m- isomer was the most active, and the activity of the o- and p- isomers was completely abolished. He generalized from this that those compounds which were derivatives of the least acidic phenols had the highest physiological activity. These compounds were also tested for their inhibitory effect on the activity of liver esterases (9), and while many of them were active in this respect, the activities did not necesarily correspond to their miotic properties.

Haworth (2) prepared and investigated a number of these compounds, and found that the features necessary for high toxicity were:

1. Replacement of one of the hydrogen atoms on the amide group by a methyl group. (In distinction to the choline type compounds).
2. Meta-orientation of the substituents.
3. Quaternary salts are generally more active than the corresponding tertiary amines, and the methiodides are more active than the hydrochlorides.

It will be noted that in physostigmine the urethane group is

para to the dialkylamino group, while the most active compounds described above were the meta-isomers. Stevens and Beutel (11) thought that the activity of physostigmine might be due to the alkyl substituent in the ring, ortho to the dialkylamino group, and prepared a series of compounds of type IV and V. They found

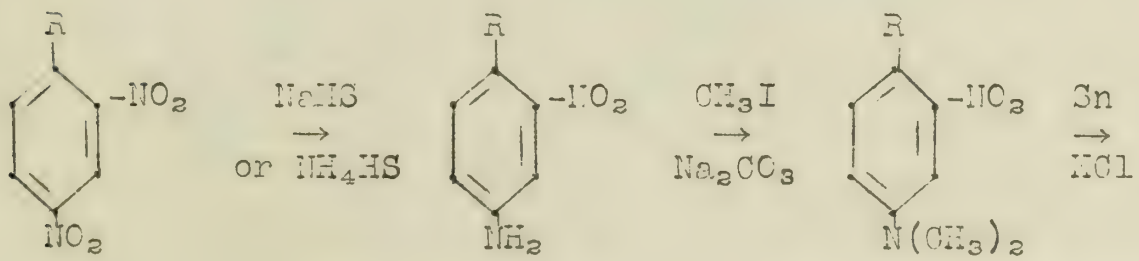


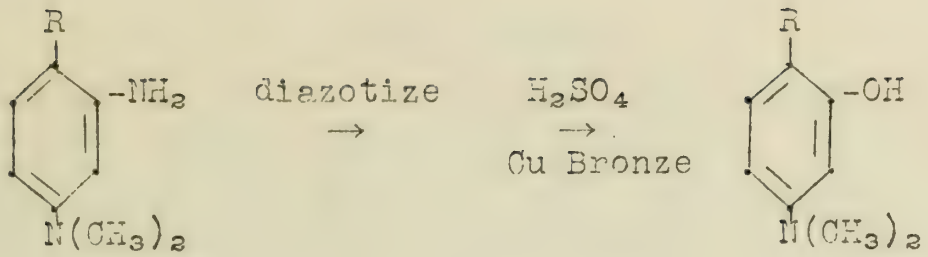
IV V

that alkyl groups in the ring, particularly isoproply, have a marked effect, increasing the toxicity in many cases from 100 to 1000 times. Haworth (2) extended this work to include the nuclear alkylated m-dimethylaminophenol derivatives, and arrived at the following generalities concerning nuclear substitution in the meta-compounds.

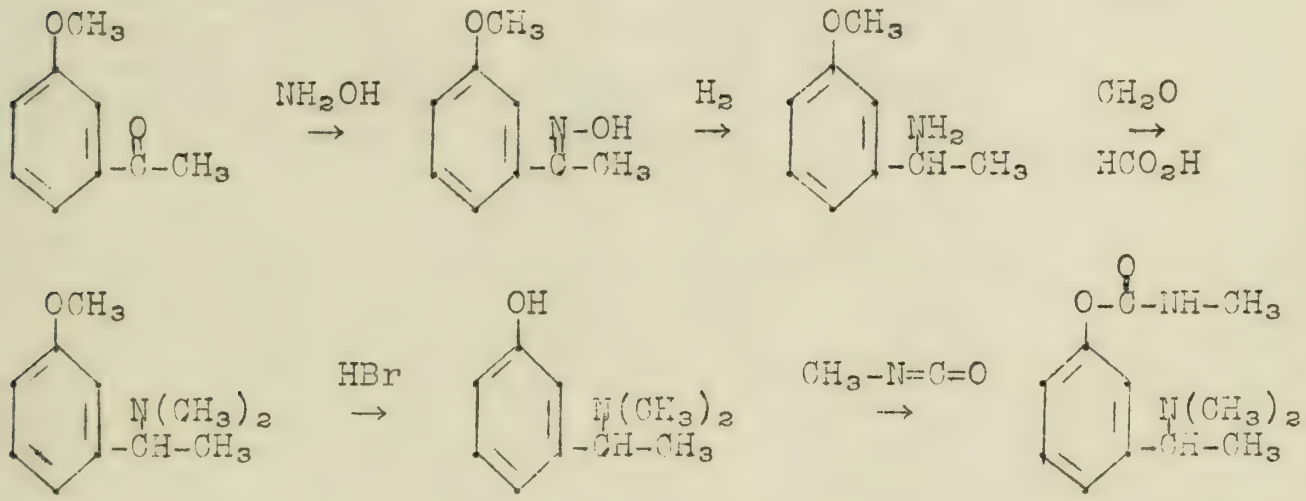
1. The presence of methyl groups increases the activity much more in the para compounds than in the meta.
2. Maximum activity is obtained with one or more methyl groups in the ring.
3. Ethyl, isopropyl, or cyclohexyl groups decrease the toxicity.
4. Position of the methyl group is unimportant, while position of the isopropyl group has enormous influence.
5. Substitution of ethyl for methyl groups on the amino nitrogen atom is of secondary importance.

These nuclear-alkylated dimethylaminophenols were generally prepared as follows.





Stedman (8) first investigated compounds of type III. A typical example of their preparation is the synthesis of "miotine".



"Miotine"

Stedman later resolved "miotine" into the d- and l-isomers, and found that the l-isomer had the higher toxicity of the two.

Haworth (3) prepared the hydrochlorides and methiodides of a number of these compounds, and also the ortho and para analogs, and compounds with additional $-CH_2-$ groups between the benzene ring and the dimethylamino group. His findings concerning their toxicity is as follows.

1. The methiodides are in practically all cases less toxic than those of the dimethylaminophenol series.
2. The hydrochlorides, as a general rule, are not very toxic. An exception to this is the hydrochloride of "miotine", which was one of the most toxic substances tested.
3. Meta-orientation of the phenolic group to the sidechain favors high toxicity.
4. The hydrochlorides are frequently more toxic than the methiodides, in contrast to the dimethylaminophenol series.
5. Alkylation of the sidechain tends to increase activity.
6. Nuclear alkylation has little effect in the ortho series and probably decreases the activity in the meta and para compounds.

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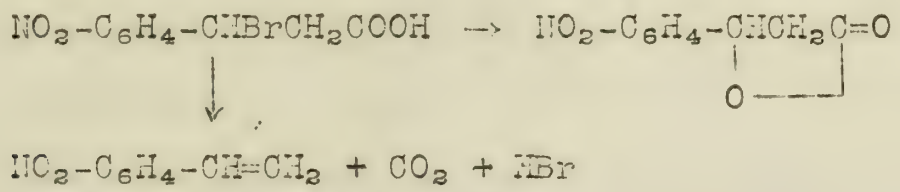
Reported by Donald L. Felley
November 21, 1947

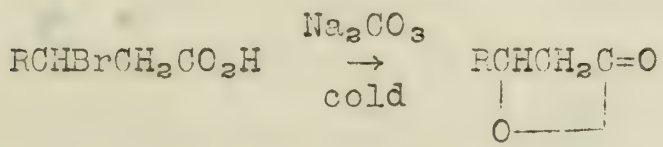
PREPARATION AND REACTIONS OF β-LACTONES

I. Discovery.--The first β-lactones were prepared by Einhorn (1), who in 1883 treated β-bromo-o-nitrophenyl propionic acid with dilute sodium carbonate and was able to isolate this new type of compound. Three years earlier, Erlenmeyer (2) had proposed that the alkenes, which were always formed by the same treatment of β-bromo acids, resulted from the preferential decomposition of intermediate β-lactones. Basler (3) followed up immediately on Einhorn's discovery and isolated the p-nitro isomer. Much later - in 1922 - Johannson and Hagman (4) proved without doubt that the alkenes are formed simultaneously with the β-lactones, and not from them. Michael and Ross (5) in 1933 sought the reason for this in the stereo structure of beta-halo acids.

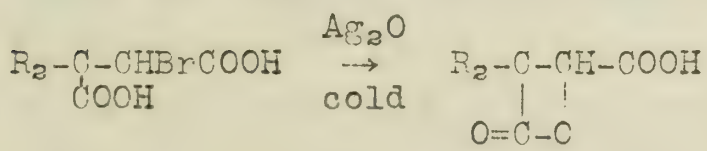


II. Preparation.--Many β-lactones are known at the present time. Those with more than four carbons are well defined, crystalline solids, stable at ordinary temperatures if kept dry. Three general methods of preparation are as follows:

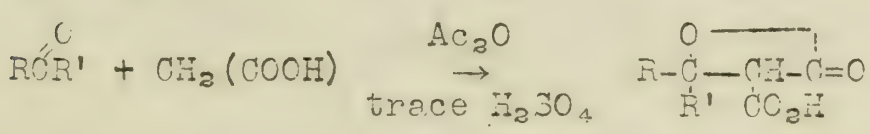
A. Einhorn (1)



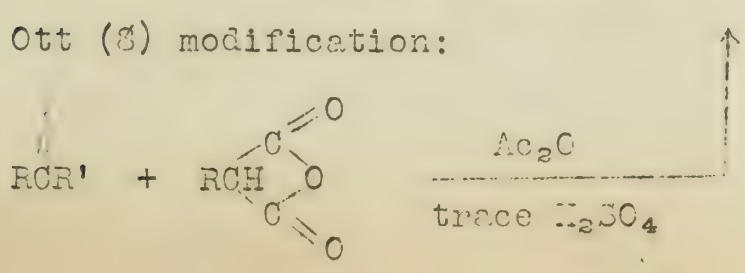
B. Baeyer and Villiger (6)



C. Meldrum (7)



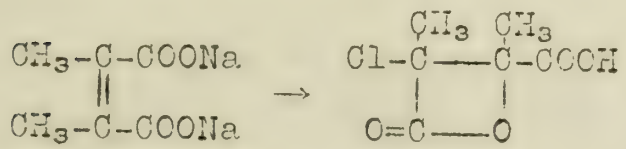
Ott (8) modification:



Yields by these procedures run from 9% for the liquid β-propiolactone (9) to 90% for the α-phenyl-β-hydroxy-β-benzoyl propionic acid lactone (10). In using the β-bromo acid, it is necessary to keep it in large excess (11) over the added sodium carbonate, and almost invariably silver oxide is required when succinic acid derivatives are involved.

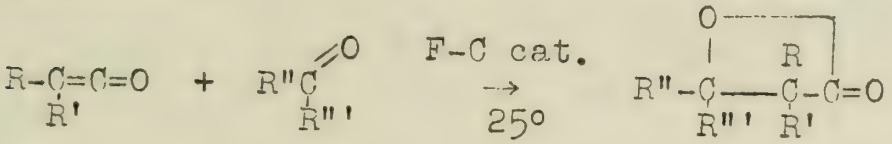
Special Preparations:

D. Tarbell and Bartlett (12) found that chlorine water or bromine water was sufficient to cause β-lactone formation from the following sodium salt:



They attribute the ease of formation to the methyl groups present, which is a tendency frequently observed.

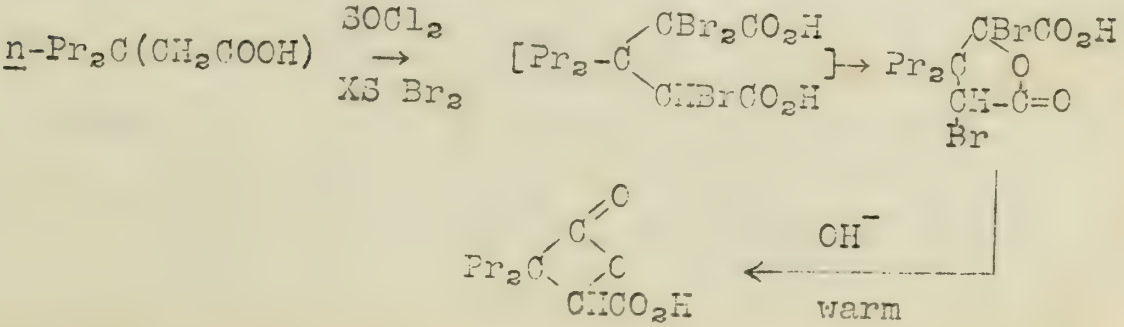
E. A recent patent by Kung (13) describes a procedure using ketenes:



R=H or alkyl free of unsaturation

Steadman (14) in 1947 received a patent for the preparation of β-propiolactone by adding to a solution of previously prepared β-lactone - at a temperature below 30°C. - ketene and formaldehyde, which yields additional propiolactone without large amounts of side products. Catalyst: aluminum chloride-zinc chloride in 1-0.5 ratio by weight.

F. Bains and Thorpe (15) have prepared a substituted malic acid lactone by a variation of "A":



warm

III. Characteristic Reactions.--

Hydrolysis:

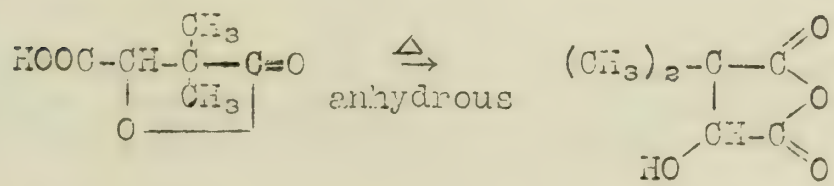
Johannson has concluded that the primary difference between γ- and β-lactones lies in the irreversibility of the reaction of the latter with water to form the corresponding hydroxy acids. This occurs in the presence of strong base very rapidly. One exception only has been noted. As-di-n-propyl-malolactone is reported to form the hydroxy acid by boiling for 1 1/2 hours in 10% sodium hydroxide, and the hydroxy-acid salt in turn to reform the lactone when acidified at 0° (15).

Titration:

Lactonic acids, as expected, titrate accurately in the cold as monobasic, and in the hot as dibasic - with definite end-points (16).

Heat:

β-lactones are unstable to heat, both in the presence of water and in anhydrous condition. No rules are available for the decomposition in any specific case. However, substituted dibasic acid lactones in the absence of water are converted by pyrolysis or vacuum distillation into the isomeric hydroxy anhydrides - the 5-membered ring being more stable as expected (16).



In all other cases, the investigators report an extensive variation of degradation products. The typical reactions are summarized below:

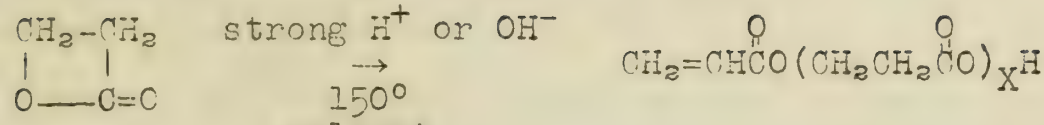
A. $RCR'CH_2C{=}O \rightarrow RCR'{=}CHCO_2H$

B. $RCH{-}CH_2 \rightarrow RCH{=}CH_2 + CO_2$

C. $(CH_3)_2{-}C{-}CH{-}CO_2H \rightarrow CH_3CCH_3 + [CHCO_2H] \rightarrow C{=}C{=}C$

$(CH_3)_2{-}C{-}C(CH_3){-}CO_2CH_3 \rightarrow CH_3CCH_3 + (CH_3)_2C{=}C{=}O$

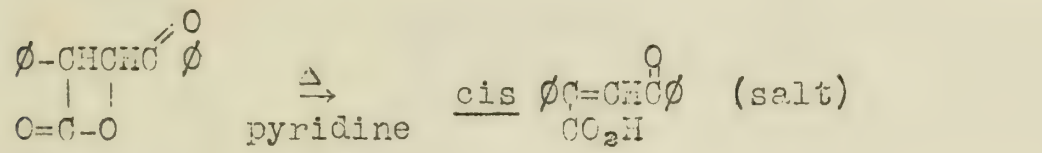
D. Polymerization



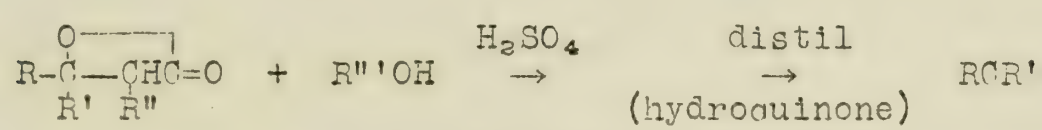
Gresham (17) (A.C.S. meeting).

Reaction "A" occurs chiefly on unsubstituted hydroxy dibasic acids. Reaction "B" occurs in most other cases, plus fragments of all kinds. Reaction "C" was reported by Ott (8) and is probably responsible for the Kung patented process already described. An attempt to explain the ketone and the carbon dioxide cleavage was made by Salkowski (18) in 1922, but extensive supporting evidence is lacking.

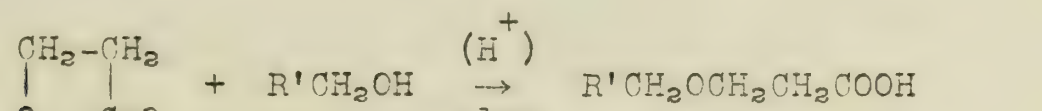
IV. General Reactions.--With ammonia or aniline, β-lactones form the hydroxy amide and anilide respectively. However, Basler (3) has reported that he found the amino groups replacing the hydroxy group. No reaction occurs with pyridine in the cold, but if the mixture is heated to 100°, the product is always the cis unsaturated acid regardless of the lactone configuration (9).

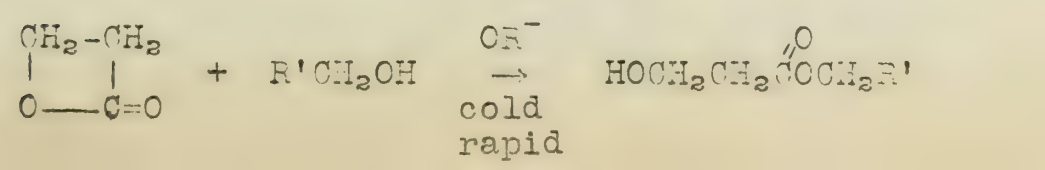


The β-bromo acid is reformed with aqueous concentrated HBr, and the same reagent plus an alcohol forms the β-bromo ester (19). Kung (20) has patented the following reaction:



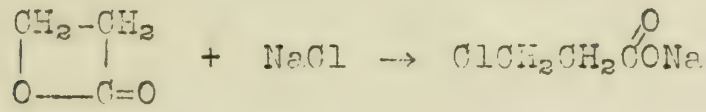
At the 112th A.C.S. meeting, Beears (21) described further alcohol reactions:



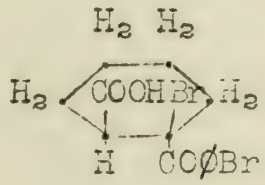


Additional products are polyester acids with alkoxy end groups, and esters of polyester acids.

A patent (22) has been issued for the reaction of $SOCl_2$ with β-propiolactone to yield the β-chloropropionyl chloride in 87-95% yield. PCl_5 in CCl_4 gives 93% yield. Salts of inorganic acids form β-halo acid salts and higher analogs according to Gregory (23). The tendency to polymerize decreases in the order NaCl, NaBr, NaI.



V. Stereochemical Considerations.--Kohler and coworkers (24) have published data on configurations in ketonic β-lactones. Since only a single lactone could be formed and that from the cis isomer of the following compound (whose configuration was known,



it was concluded no Walden inversion occurs in ring formation. This is supported by polarimetric data of Bickel (25). The opening of the ring, however, may or may not be accompanied by inversion, depending on the type of compound and reagent used. No generalization on ring opening is available at present.

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Reported by T. E. Bockstahler
November 21, 1947

REACTIONS OF ORGANOMETALLIC COMPOUNDS

Introduction.--Although they are hardly mentioned in connection with organometallic compounds, ethers do enter into many interesting reactions with organometallic compound. Recent work by Lüttringhaus (3,4,5,6) has emphasized their importance. They may be classified as follows.

I. Simple Ether Cleavage

$$R\text{-}O\text{-}R' + R''Me \rightarrow ROMe + R'\text{-}R''$$

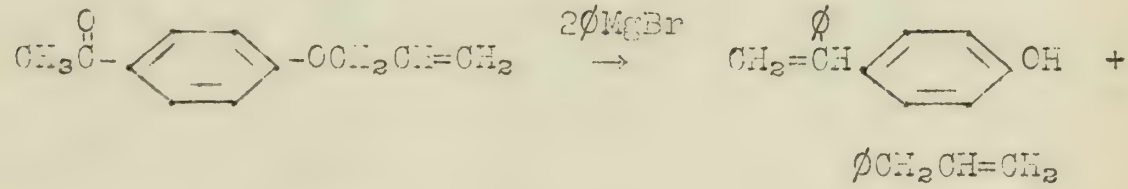
Examples:

1. $\emptyset\text{-}O\text{-}CH_2\text{-}CH{=}CH_2 + RMgX \rightarrow \emptyset OMgX + \emptyset CH_2\text{-}CH{=}CH_2$

2. $2\ \emptyset\text{-}O\text{-}CH_2\text{-}CH{=}CH_2 + Mg(\emptyset)_2 \xrightarrow[6\ \text{hrs.}]{75} \xrightarrow{NH_4Cl} \emptyset OH + \emptyset CH_2CH{=}CH_2$

3. $\underline{n}\text{-}C_8H_{17}\text{-}O\text{-}CH_2CH{=}CH_2 + \emptyset MgBr \rightarrow \emptyset CH_2CH{=}CH_2 + C_8H_{17}OH$ (85%)

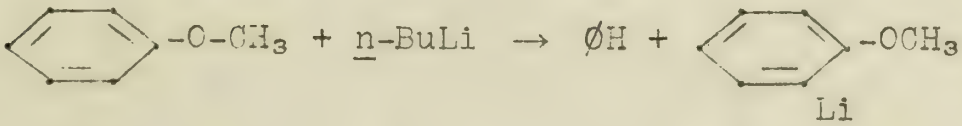
4. Aryl allyl thio ethers react similarly but alkyl allyl thio ethers do not react.

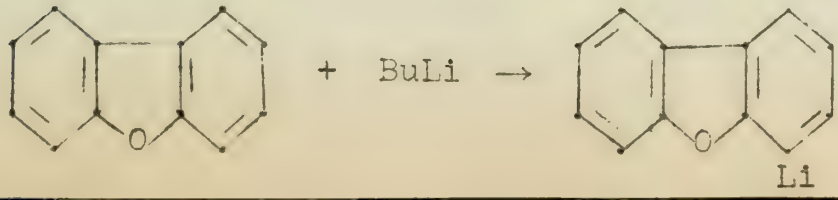
5. 

II. Simple Metal Substitution

A. Exchange of the <u>ortho</u> hydrogen in the aryl part

Examples:

1.  (1)

2.  (2)

B. Exchange in the alkyl part

Examples:

$\emptyset SCH_3 + \underline{n}\text{-BuLi} \rightarrow \emptyset SCH_2Li$ (1)

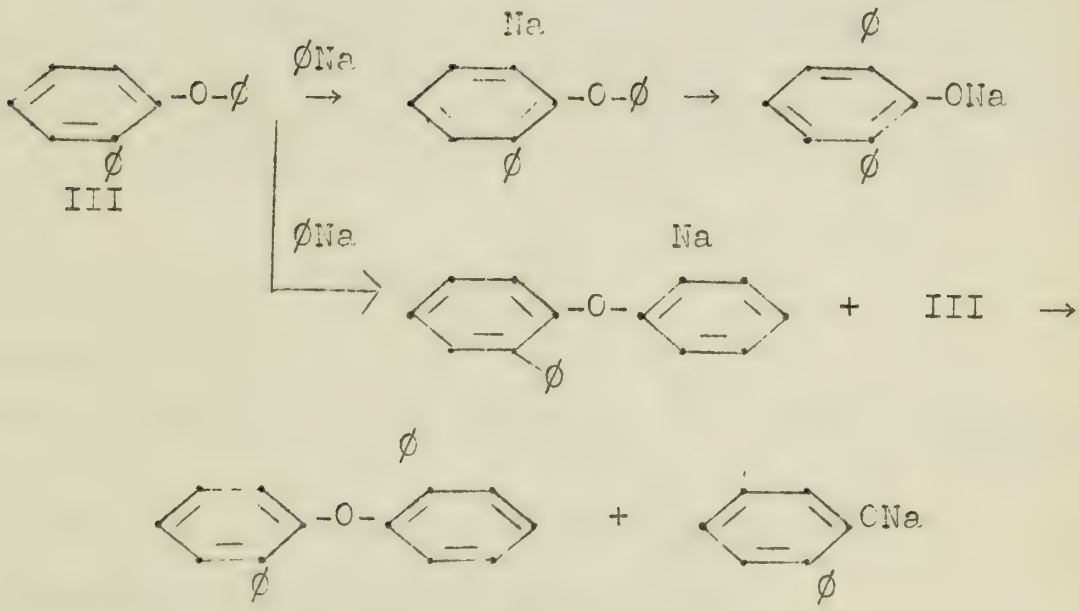
III. Hydrogen-Metal Exchange followed by Other Reactions

A. Ether Cleavage and Rearrangement

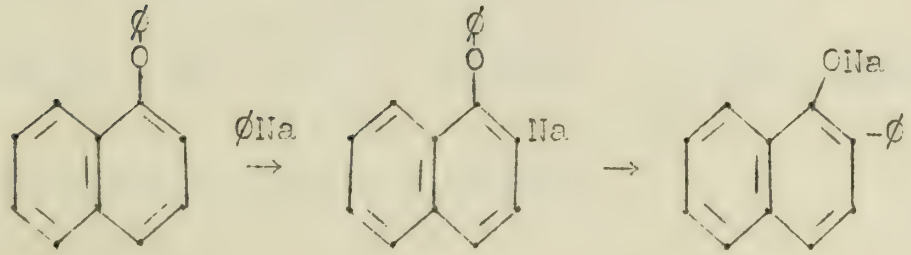
1. In the aryl part

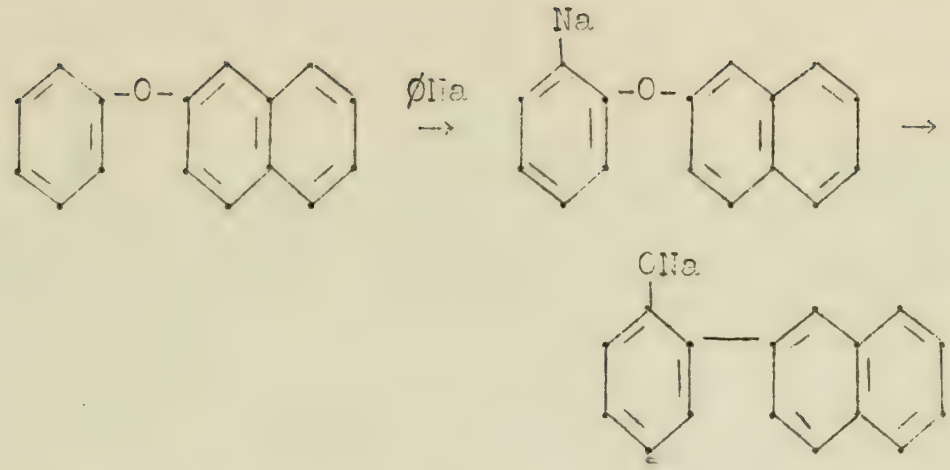
Examples:

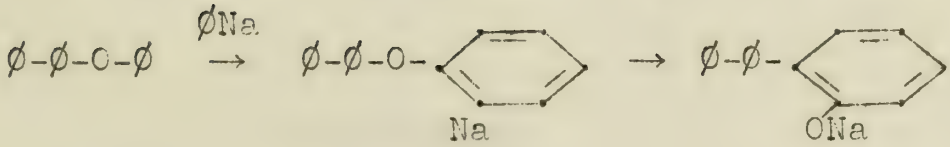
1. $\underset{\text{I}}{\emptyset\text{-O-}\emptyset} + \emptyset Na \rightarrow \emptyset H + \underset{\text{II}}{\emptyset\text{-O-}C_6H_4\text{-}Na} \xrightarrow{\emptyset\text{-O-}\emptyset} \underset{\text{III}}{\emptyset\text{-O-}C_6H_4\text{-}\emptyset} + NaO\emptyset$



2.



3. 

4. 

5. 

In these reactions, the primary reaction is the Na-hydrogen substitution. Then the splitting occurs. The ortho sodium compounds are obtainable but are short lived at room temperature. The authors believe that the mechanism of this reaction is simply the rearrangement of the anion with the phenyl nucleus seeking the negative center ortho to the oxygen and then the sodium attaching itself to the oxygen.

2. Exchange in the alkyl part

Examples:

1. $\text{Ø-O-CH}_2\text{-Ø} + \text{ØLi} \rightarrow \text{Ø-O-CH-Ø} \xrightarrow{\text{ØLi}} \text{ØOLi} + \text{Ø}_2\text{CHLi}$
   (Li)

   $\text{Ø}_2\text{CHLi} + \text{Ø-O-CH}_2\text{-Ø} \rightarrow \text{Ø}_2\text{CH-CH}_2\text{Ø} + \text{ØOLi}$

2. Preparation of diphenyl malonic acid

   $\text{Ø}_2\text{CH}_2 + \text{ØLi} \xrightarrow[\text{6 hrs.}]{80} \text{Ø}_2\text{CLi}_2 \xrightarrow[\text{CO}_2]{} \text{Ø}_2\text{C-(COOH)}_2$

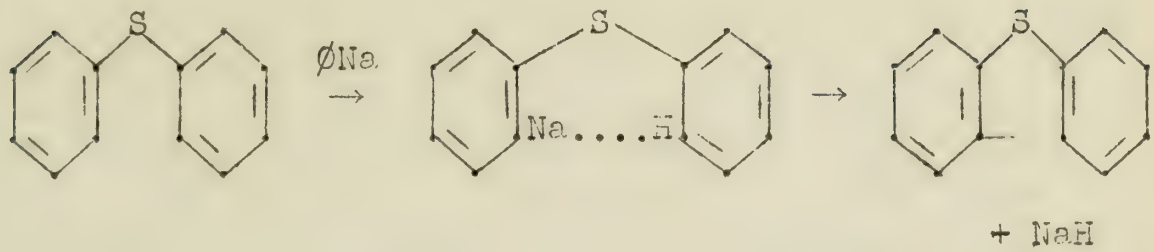
B. Followed by Olefin Cleavage

Examples:

$\text{Ø-CH}_2\text{-O-CH}_2\text{CH}_3 + \text{ØLi} \rightarrow \text{Ø-C-O-CH}_2\text{CH}_3 \rightarrow \text{ØCH}_2\text{Li} + \text{CH}_2\text{=CH}_2$ (7)

C. Followed by Ring Closure

Examples:



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Reported by Joseph R. Gordon
November 21, 1947

PERFORMIC ACID AS A HYDROXYLATING AGENT

The availability of more concentrated solutions of hydrogen peroxide once again has called attention to the peracid oxidation of olefinic double bonds, since the aliphatic peroxides conceivably can be used industrially in the preparation of dihydroxy fatty acids from mono-unsaturated ones. These substances are of interest in the preparation of alkyd-type resins and plasticizers. The hydroxylation of terpenes, unsaturated oils, and rubbers gives rise to compounds which are of interest commercially (1).

The reaction of an aliphatic acid and hydrogen peroxide to form the peracid is reversible, and will go to completion if the peracid is allowed to react with some oxidizable material. The oxidation reaction is fairly rapid, while the formation of the peracid, in most cases, is very slow at ordinary temperatures unless catalyzed (2). For instance, the reaction of oleic acid with hydrogen peroxide in acetic acid requires a week at room temperature with considerable loss of active oxygen through decomposition of the hydrogen peroxide. Raising the temperature increases the reaction rate, but also aggravates the loss of oxygen through decomposition.

Unlike the other aliphatic acids, formic acid reacts rapidly with hydrogen peroxide to form performic acid even at moderate temperatures. With formic acid and 30% hydrogen peroxide, the maximum concentration of performic acid (4.7%) is attained in 2 hours, while with 90% hydrogen peroxide, the maximum (35.8%) is reached in 30 minutes. Compare this to acetic acid, which with 30% hydrogen peroxide gives a maximum of 8.6% in 80 to 90 hours, and with 90% hydrogen peroxide, a maximum of 46% in 12 to 15 hours (3). Thus the reaction of hydrogen peroxide and formic acid with oleic acid is complete in 2 to 4 hours at room temperature. The short reaction time and low temperature result in the loss of little active oxygen through decomposition and consequently the hydrogen peroxide is used in almost stoichiometric amounts. The rapid reaction time is not due entirely to the greater acidity of formic acid (ionization constant 1.8×10^{-4} compared to 1.8×10^{-5} for acetic acid), since its rate of formation is still three times that of peracetic acid in a reaction catalyzed by 1% sulfuric acid.

From analogy to oxidation reactions carried out with peracetic and perbenzoic acids, one would expect to find some epoxy compounds formed with performic acid. Actually, even at low temperatures, hydroxy-formoxy derivatives were formed almost quantitatively which yielded upon saponification quantitative amounts of the dihydroxy products. The fact that the greater acidity of formic acid is responsible for this result was demonstrated by the observation that peracetic acid, itself, yielded epoxy derivatives, but when made more acidic by 1% sulfuric acid, hydroxy-acetoxy derivatives were the only products. It is probable that the epoxy compounds are formed as intermediates and then hydrolyzed, as indicated in the reaction postulated by King (6), and by Swern, Billen, and Scanlon (2):

$$R_1COOH + H_2O_2 \rightleftarrows R_1COO_2H + H_2O$$

$$R_2CH{=}CH{-}R_3 + R_1COO_2H \rightarrow [R_2{-}\underset{\diagdown O \diagup}{CH{-}CH}{-}R_3 + R_1COOH] \rightarrow R_2{-}\underset{H}{\underset{|}{C}}H{-}\underset{COR_1}{\underset{|}{C}}H{-}R_3$$

$$R_2{-}\underset{H}{\underset{|}{C}}H{-}\underset{COR_1}{\underset{|}{C}}H{-}R_3 + H_2O \rightarrow R_2{-}\underset{H}{\underset{|}{C}}H{-}\underset{H}{\underset{|}{C}}H{-}R_3 + R_1COOH$$

Besides giving almost quantitative yields of dihydroxy compounds from mono-unsaturated substances like oleic and elaidic acids and oleyl alcohol (2), performic acid has been used to give from 46 to 51% yields of α,β-dihydroxy acids from α-unsaturated acids and esters (4). This reagent was used with 1-olefins, giving 70 to 100% yields of the 1,2-diols after a reaction time of 24 hours (5). The longer time was necessary because of the lesser solubility of the hydrocarbons in the reaction mixture. In all cases, the reaction was completed 1 to 2 hours after the reaction mixture became homogeneous.

Some advantages in using performic acid as an oxidizing reagent are:

1. High reaction efficiency.
2. Minimum by-product formation.
3. Lack of metallic contamination.
4. General solubility of oxidizing agent in reaction medium.
5. Ease of preparation of performic acid.

One disadvantage to the use of performic acid is the danger entailed in handling concentrated hydrogen peroxide. By itself, hydrogen peroxide is not explosive, but it forms shock-sensitive mixtures with certain compounds.

COMPARISON OF VARIOUS OXIDIZING AGENTS

Starting Material	Final Product	Performic Acid			Peracetic Acid with H_2SO_4		
		Yield %	Time hours	Temp. °	Yield %	Time hours	Temp. °
Oleic acid*	9,10-dihydroxy-stearic acid	99	2	40	95	6	40
Elaidic acid**	9,10-dihydroxy-stearic acid	99	2	40	78	5	40
Oleyl alcohol	9,10-dihydroxy-octadecanol-1	100	2 1/2	40	46	4 1/2	25
1-Octene	Octanediol-1,2	70	24	40	50	28	40

COMPARISON OF VARIOUS OXIDIZING AGENTS (CONTINUED)

Starting Material	Final Product	Performic Acid Yield %	Performic Acid Time hours	Performic Acid Temp. °	Peracetic Acid with H_2SO_4 Yield %	Peracetic Acid with H_2SO_4 Time hours	Peracetic Acid with H_2SO_4 Temp. °
1-Decene	Decanediol-1,2	75	24	40	60	28	40
1-Dodecene	Dodecanediol-1,2	75	24	40	60	28	40
1-Tetradecene	Tetradecanediol-1,2	95	24	40	60	28	40
1-Hexadecene	Hexadecanediol-1,2	100	24	40	56	28	40
1-Octadecene	Octadecanediol-1,2	100	24	40	41	28	40
2-Nonenoic acid	α,β-Dihydroxypelargonic acid	51	2	60			
2-Undecenoic acid	α,β-Dihydroxyundecanoic acid	46	3/4	60			

*Osmium tetroxide with hydrogen peroxide in t-butyl alcohol gives 60% yield of the product in 24 hours at 0°; peracetic acid alone gives 45% yield in 9 days at 25°; alkaline potassium permanganate gives a 96% yield in 5 minutes at 0°; and perbenzoic acid takes 5 days at 25°.

**Peracetic acid alone gives a 32% yield in 6 days at 25°, while perbenzoic acid takes 3 days at 25°.

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Reported by Eric Barthel
November 21, 1947

ACID-CATALYZED ADDITION OF ALKYL HALIDES TO OLEFINS

Addition reactions of certain polychloroalkanes, particularly chloroform and carbon tetrachloride, with chlorinated olefins in the presence of aluminum chloride have been known since 1911 (1,2). Condensations of this type,

$$(1)\quad CCl_2 = CCl_2 + CHCl_3 \xrightarrow{AlCl_3} CCl_3\text{-}CCl_2\text{-}CHCl_2 \qquad 88\text{-}93\%$$

$$(2)\quad CCl_2 = CHCl + CCl_4 \xrightarrow{AlCl_3} CCl_3\text{-}CHCl\text{-}CCl_3 \qquad 49\%$$

referred to as the Prins reaction, have been reviewed (3). It was believed that the reaction is of limited applicability, occurring only between polychloroalkanes and polychloroölefins.

Recently, it has been found that a proper choice of conditions and catalysts may effect the addition of alkyl halides (monohaloalkanes) to chlorosubstituted or to unsubstituted olefins. The reaction takes place in the presence of catalysts ($AlCl_3$, $FeCl_3$, $BiCl_3$, BF_3) of the Friedel-Crafts type. In general, the primary reaction involves the addition of the halogen atom and the alkyl fragment across the double bond of the olefin, the addition obeying Markownikoff's rule.

Reactants.--Olefins which have been employed are ethene, propene, cyclohexene, 2-butene, vinyl chloride, allyl chloride, 2-chloropropene, 1,2-dichloroethene and dichloropropenes. The alkyl halides thus far studied are t-butyl, t-amyl, isopropyl, n-propyl, sec.-butyl, and isobutyl chlorides. Ethyl and methyl chlorides did not react in attempted additions to monohaloölefins. Tert.-butyl chloride condensed with all of the olefins listed.

Conditions.--The reaction conditions depend both on the catalyst and the reactants used. Thus, low temperatures, for example -30 to 0°, are preferred for an active catalyst as aluminum chloride. Less active catalysts as bismuth chloride or zinc chloride may require temperatures as high as 100°.

Products.--These reactions are usually complicated by the production of at least one secondary product in addition to the primary compound.

Unsubstituted Olefins.--The condensation of t-butyl and t-amyl chlorides with ethene (4a) and with propene (5) give typical primary addition products.

$$(3)\quad (CH_3)_3CCl + CH_2{=}CH_2 \xrightarrow[-25 \text{ to } -10^\circ]{AlCl_3} (CH_3)_3C\text{-}CH_2CH_2Cl \qquad 75\%$$

I

$$(4)\quad C_2H_5C(CH_3)_2Cl + CH_2{=}CH_2 \xrightarrow[-10 \text{ to } -2^\circ]{AlCl_3} C_2H_5C(CH_3)_2CH_2CH_2Cl$$

II 25%

The secondary products of reactions (3) and (4) are 1-chloro-3,3-dimethylpentane (II) and 1-chloro-3,3-dimethylbutane (I), respectively.

Yields with primary and secondary halides were low; alkyl halide was recovered. Both n-propyl and isopropyl chlorides with ethylene gave, not the expected amyl chlorides, but 1-chloro-3,3-dimethylpentane, the product of reaction of t-amyl chloride with ethylene.

$$(5)\quad (CH_3)_2CHCl + CH_2{=}CH_2 \xrightarrow{AlCl_3} [(CH_3)_2CHCH_2CH_2Cl]$$

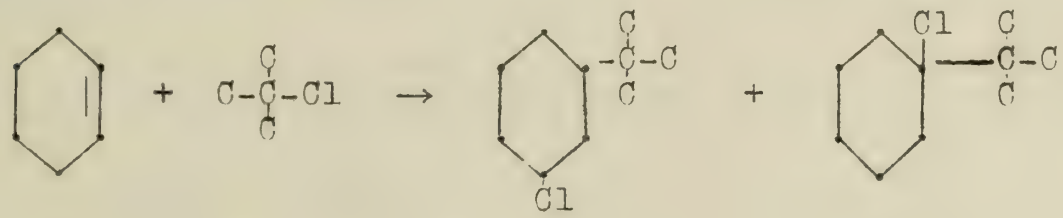
$$\downarrow$$

$$CH_3CH_2C(CH_3)_2CH_2CH_2Cl \longleftarrow [(CH_3)_2\text{-}CHCl\text{-}CH_2CH_3]$$

II

A similar reaction was observed with sec.-butyl and isobutyl chlorides.

The alkylation of cyclohexene with t-butyl chloride is abnormal (4b) and with aluminum chloride as catalyst at -25 to -15° proceeds as follows:

(b) 

III IV

85% of product 15% of product

Variation in temperature and catalyst results in changing the proportions of the two products.

Monohaloölefins (4c).--Examples are listed below:

$$(7)\quad CH_2{=}CHCl + (CH_3)_2CHCl \xrightarrow[-30 \text{ to } -20^\circ]{AlCl_3} CHCl_2\text{-}CH_2\text{-}CH(CH_3)_2$$

34%

$$(8)\ CH_2{=}CHCl + (CH_3)_3CCl \xrightarrow[\text{R. T.}]{FeCl_3} CHCl_2{-}CH_2{-}C(CH_3)_3 \qquad 77\%$$

$$(9)\ CH_2{=}CHCl + C_2H_5C(CH_3)_2Cl \xrightarrow[-20 \text{ to } 0^\circ]{AlCl_3} CHCl_2{-}CH_2{-}C(CH_3)_2C_2H_5 \qquad 38\%$$

The dichloro products yield the corresponding aldehydes on hydrolysis.

With 2-chloropropene and with allyl halides, tertiary alkyl chlorides form 2,2-dichloro-4,4-dimethylalkanes and 1,2-dihalo-4,4-dimethylalkanes, respectively. The 2,2-dichloro-4,4-dimethylalkanes offer a possible route to methyl neoalkyl ketones; while the 1,2-dihalo-4,4-dimethylalkanes may be used to synthesize pure alkenes and, thence, alkanes.

Polychloroölefins (4d).--n-Propyl and isopropyl chlorides add to sym.-dichloroethylene to give the same trichloropentane. The yield is about twice as great from cis-dichloroethylene as from the trans compound. Even more striking is the 75% yield obtained from t-butyl chloride with cis-dichloroethylene compared to a 2% yield with the trans isomer.

Mechanism.--The mechanism may be postulated as that of addition to carbon-carbon double bonds. The acid catalyst promotes an actual or virtual carbonium ion intermediate. The action of t-butyl chloride on 2-chloropropene illustrates some of the possibilities.

$$(CH_3)_3CCl + AlCl_3 \rightarrow (CH_3)_3C^+AlCl_4^-$$

$$(CH_3)_3C^+ + CH_3 \rightarrow C(:\ddot{Cl}:) = CH_2 \rightarrow (CH_3)_3C{-}CH_2{-}\overset{+}{C}Cl{-}CH_3$$

$$(CH_3)_3C{-}CH_2{-}\overset{+}{C}Cl{-}CH_3 \xrightarrow{CH_3CCl=CH_2} (CH_3)_3CCH_2{-}\underset{CH_3}{\underset{|}{C}}(Cl){-}CH_2{-}\overset{+}{C}(Cl){-}CH_3$$

$$\downarrow \qquad\qquad\qquad \downarrow$$

$$(CH_3)_3C{-}CH_2{-}CCl_2{-}CH_3 \qquad\qquad (CH_3)_3C{-}CH_2{-}\underset{CH_3}{\underset{|}{C}}(Cl){-}CH_2{-}\underset{Cl}{\underset{|}{C}}(Cl){-}CH_3$$

49% V 19% VI

With $BiCl_3$ at 50°, instead of VI, a by-product is formed by the elimination of a proton.

$$(CH_3)_3CCH_2\overset{+}{C}ClCH_3 \xrightarrow{-H^+} (CH_3)_3C-CH_2-CCl=CH_2$$

Rearrangement products are formed when the carbonium ion becomes involved in shifts of alkyl groups or hydrogen. Such a mechanism explains why n-propyl and isopropyl chlorides yield the same product in the two cases cited.

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Reported by Y. F. Shealy
November 21, 1947

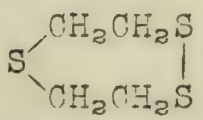
SULFURIZATION OF OLEFINS

I. Introduction.--Sulfur reacts with olefins in numerous ways which have been very much a matter of speculation until recent times. Great advances in reaction mechanisms have taken place in the past two years led by industry's investigations into the mechanism of rubber vulcanization. The reactions between sulfur and olefins seem to be conveniently divided into those taking place at high temperatures (170°C and up) and those run at the vulcanization temperature of rubber (140°C and below)

II. High Temperature Reactions.--The high temperature reactions are generally based on older work.

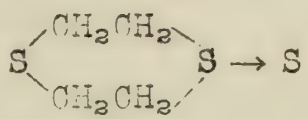
This dealt with the reaction between ethylene and sulfur at approximately 300-750°C. The products isolated included traces of thiophene and varying amounts of ethyl mercaptan, ethyl sulfide, carbon disulfide, and hydrogen sulfide. If the reaction is carefully run, intermediate products can be isolated thus indicating a relatively complicated mechanism of attack (4).

a.



or

b.



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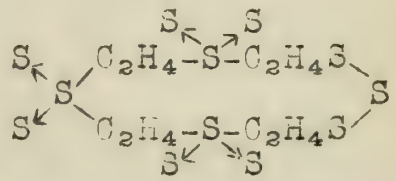


In addition to these products there was also formed a polymeric insoluble sulfide.

Recent patents have indicated the successful commercial preparation and ethanethiol, ethane dithiol, ethylthioethanethiol, and the diethyl ether of ethanedithiol (5,6,7). These were prepared by treating ethylene and sulfur with benzene as solvent under 1000 lbs. at 175°C. followed by the hydrogenation of the sulfurized product using the sulfactive catalysts such as cobalt trisulfide. Similar products have been obtained using butene-2, octene-1, and styrene as the olefins.

The formation of phenyl thiophenes from cinnamic acid or styrene and sulfur at 210° have been reported (8,9). The preparation of thiophene and its derivatives from 1,3-diolefins and sulfur was reported by Shephard, et al (16). At 320-420° butadiene yielded 6% thiophene and isoprene gave 47% of 3-methyl thiophene.

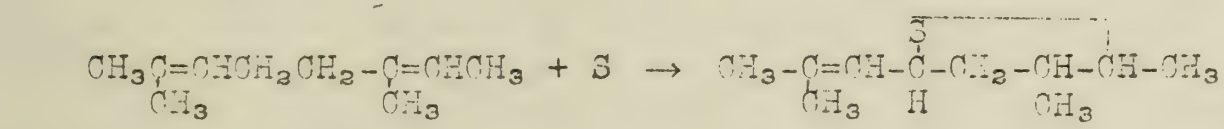
III. Recent Low Temperature Studies.--Most recent low temperature studies have been directed at obtaining a mechanism for sulfur reaction with $\Delta^{1,5}$ and $\Delta^{1,5,9}$ etc. unsaturated systems (1,2,12). Mechanisms proposed for these systems quite likely would have to be extensively altered to apply to conjugate systems ($\Delta^{1,3}$ and $\Delta^{1,3,5}$ etc.).

In general, the products obtained from the non-conjugated

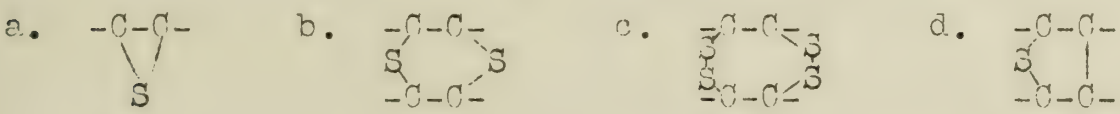
system are of the type, RS_xR', where R and R' may be saturated or unsaturated radicals derived from the olefin. The H/C ratio remains unchanged in this reaction and the numerical value of x depends somewhat upon the time of heating. Cyclohexene may be used as an example.

$$2\ C_6H_{10} \rightarrow C_6H_9S_xC_6H_{11}$$

In going to the isoprenic diolefins, the possibilities of sulfur reaction are greatly increased. The sulfur can now react both intermolecularly and intramolecularly. The latter case presumably giving a 5- or 6-membered ring. Experimentation has shown that the amount of intramolecular cyclization exceeds the cross-linking reaction in simple olefins and that all the cyclic compounds are monosulfides.

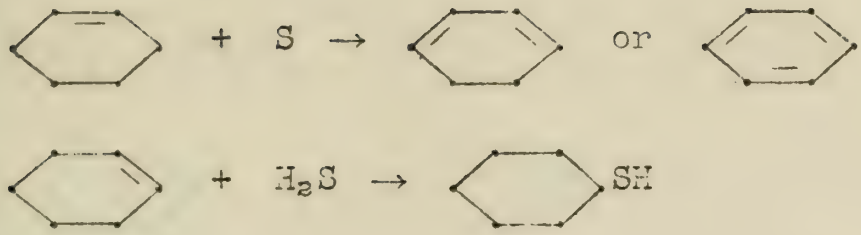


IV. Proposed Mechanism for Low Temperature Reactions with $\Delta^{1,5}$ etc. Unsaturation.--It has been generally observed in past studies on rubber vulcanization, that one double bond is destroyed for every atom of sulfur reacting and that the H/C ratio remains essentially constant. It should be pointed out in this connection, however, that the analytical methods, particularly those of a few years ago, were unsuitable for accurate determinations of differences in unsaturation between the crude rubber and the vulcanizate (1). These early observations, however, led to the postulation without proof, of a simple polar addition of sulfur to the double bond.



There are, however, few, if any, indications in organic chemistry pointing to sulfur as a polar additive agent such as the halogens, halogen acids, or ozone. Sulfur does behave similarly to oxygen in a number of cases. Modern studies of the reaction between olefins and oxygen have indicated an attack on the α-methylenic hydrogens and have given all indications of a free radical reaction.

Several investigators have confirmed the constant H/C ratio and indicated negligible amounts of hydrogen sulfide are formed in these sulfurizations (1,11,13). These factors seem to rule out the previously proposed Vesterburg dehydrogenation mechanism (a) and simple methylenic coupling (b).

a. 

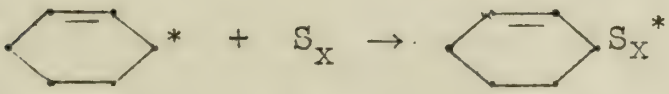
b. 

Reaction (a) would cause the formation not only of hydrogen sulfide but also of an equivalent amount of cyclohexadiene or more probably benzene and neither of these are found at the end of the reaction. Also neither of these reactions could account for the polysulfides which predominate in the reaction. In support of this, it is known that when hydrogen sulfide reacts with simple olefins, even in the presence of free sulfur, the products are almost entirely monosulfides.

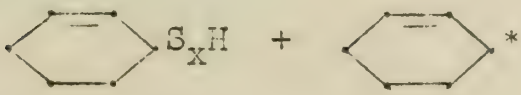
Further evidence which indicates that sulfur does not add via the hydrogen sulfide mechanism is found in studying the reaction of sulfur on dihydromyrcene, $CH_3C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_3$, which gives only the unsaturated cyclic monosulfide of the same H/C ratio. If a mercaptan were first formed and then added to the remaining double bond, the molecule would lose its unsaturation.

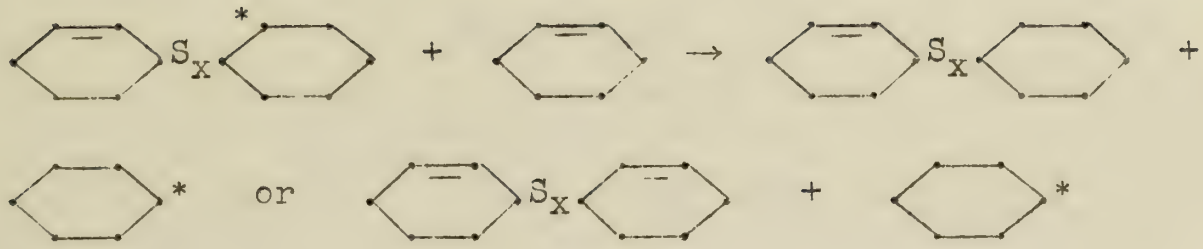
Considering that sulfur, like oxygen, has a tendency to undergo a nonpolar free radical type of reaction, Farmer has proposed the following mechanism which begins as a substitution reaction and ends by the addition of a radical at one end of a double bond (1).

(1) 

(2) 

(3) 



(4) 

There is considerable evidence supporting this theory. 2-Methyl butene-1 and 2-methyl butene-2 have been found to give the following radicals which can be conveniently explained on the basis of α-methylenic attack (11).

$$CH_2{=}\underset{CH_3}{C}{-}CH_2CH_3 \xrightarrow{S} {-}SCH_2\underset{CH_3}{C}{=}CH{-}CH_3 \;+\; {-}S{-}CH_2{-}\underset{C_2H_5}{C}{=}CH_2$$

$$CH_3{-}\underset{CH_3}{C}{=}CHCH_3 \xrightarrow{S} CH_2{=}\underset{CH_3}{C}{-}\underset{CH_3}{CH}{-}S{-} \;+\; {-}SCH_2\underset{CH_3}{C}{=}CHCH_3 \;+\; {-}SCH_2CH{=}\underset{CH_3}{C}{-}CH_3$$

It has also been noted that in the catalyzed vulcanization process for rubber, oxygen acts as an inhibitor. This further suggests a free radical mechanism rather than simple addition.

Selker and Kemp have shown by treatment of the vulcanizate with methyl iodide that the sulfur can be removed in a manner similar to the reaction with allyl sulfide (15). Their work indicates that a high percentage of the sulfur bonds are of the allyl type. This allyl linkage would be hard to explain by a simple polar addition mechanism.

This free radical theory will explain the constant H/X ratio but does not conform to the old ideas of the unsaturation loss in rubber since polysulfide linkages are indicated. This radical mechanism could be correlated to the old ideas of unsaturation only if the cross links in rubber vulcanizates are practically entirely monosulfide linkages or if there is a large amount of direct C-C, α-methylenic bonds. The latter appears to be unlikely since in desulfurization reactions using hydrogen and Raney nickel, only monomolecular hydrocarbons have been obtained. Recent investigations have shown that it is highly improbable that one double bond is destroyed for every sulfur added. The exact relation between the amount of sulfur reacted and the unsaturation loss still remains obscure.

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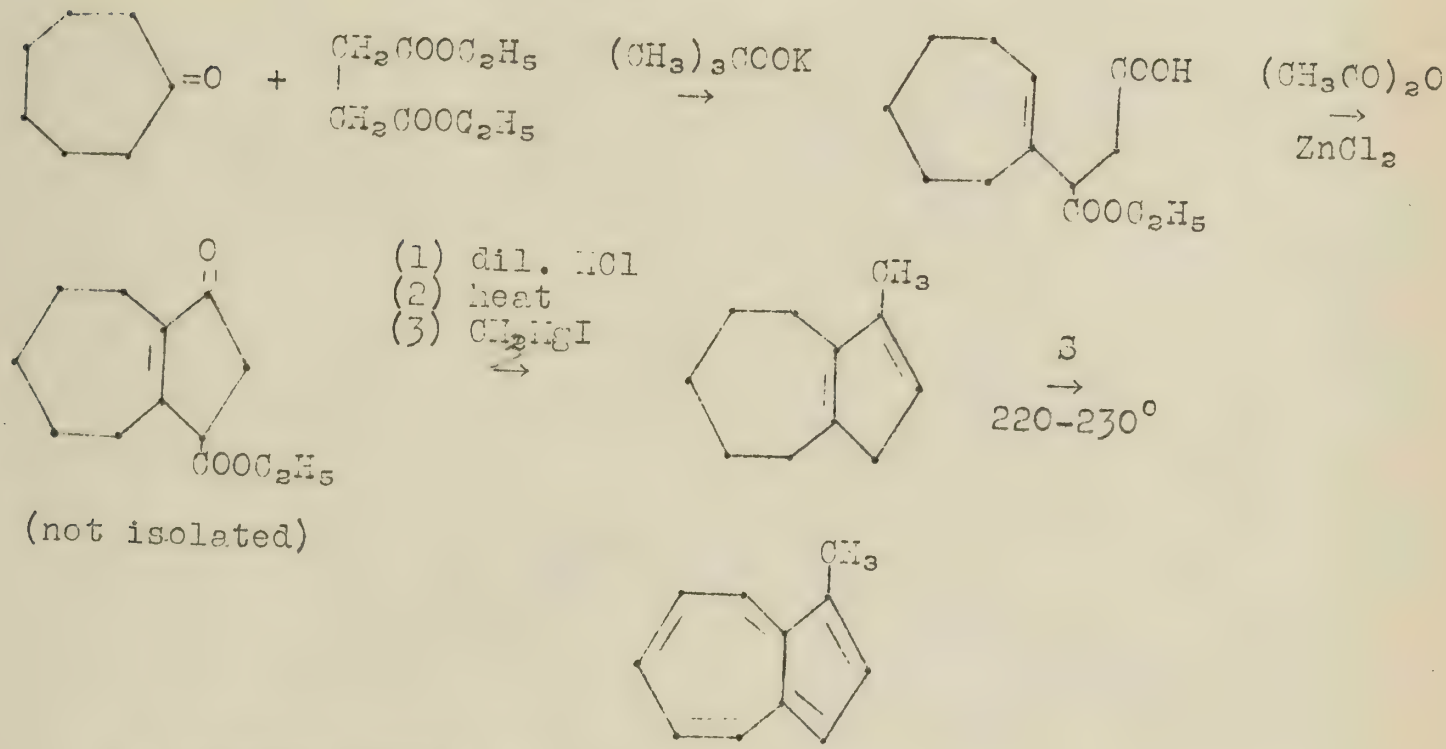
Reported by John H. Johnson
December 5, 1947

AZULENES

Azulene, as its name indicates, is a blue unsaturated hydrocarbon. In 1915 Sherndal obtained the blue component of essential oils, camillen oil, in pure form and proved it to be a liquid hydrocarbon of empirical formular $C_{15}H_{18}$. The structure remained unknown until 1936 when Pfau and Plattner started to investigate these compounds. As a result of their work, the structure of azulene has been elucidated, as a five-membered ring fused with a seven-membered ring through adjacent carbon atoms and with complete conjugation.

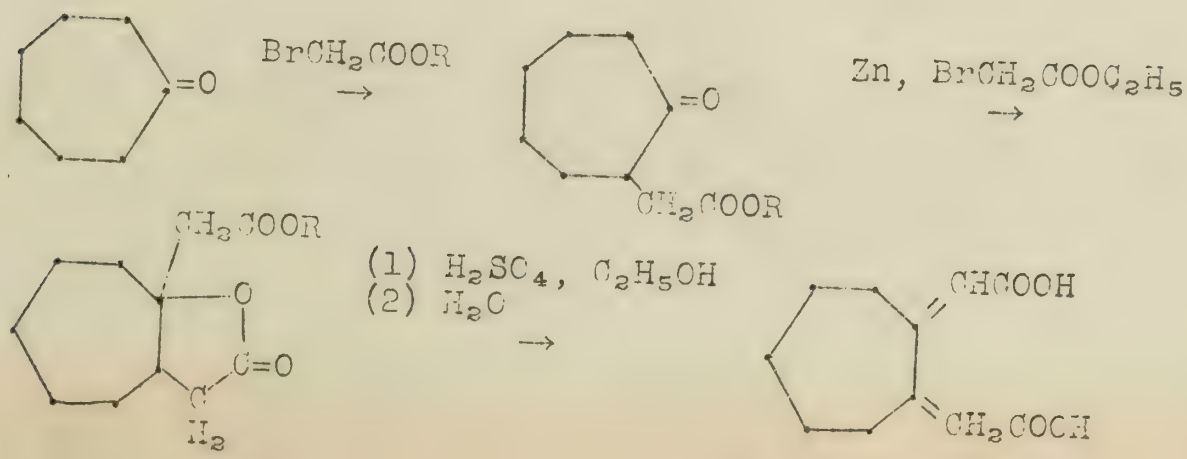
Synthetic method for preparing various substituted azulenes have been deviced, and are illustrated below.

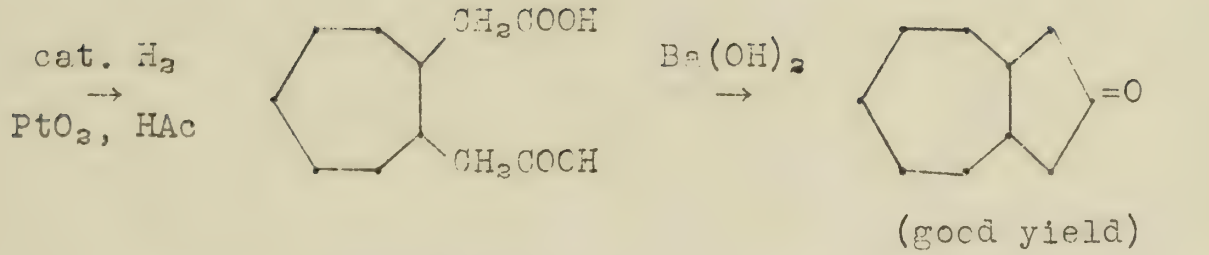
1. <u>1-Substituted Azulene</u>.--

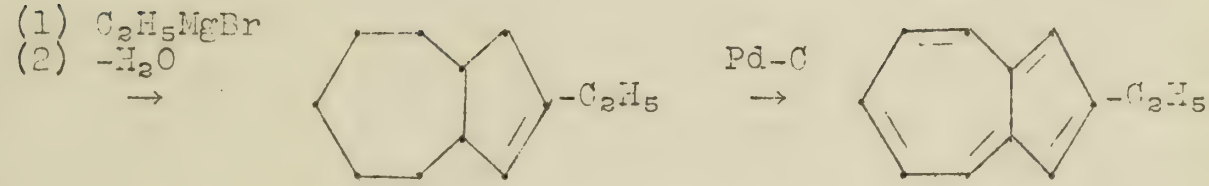


2. <u>2-Substituted Azulene</u>.--

(a)

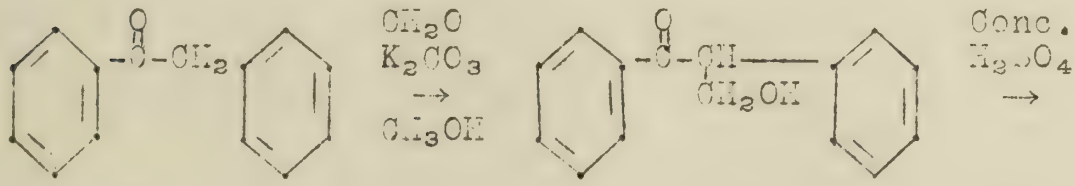


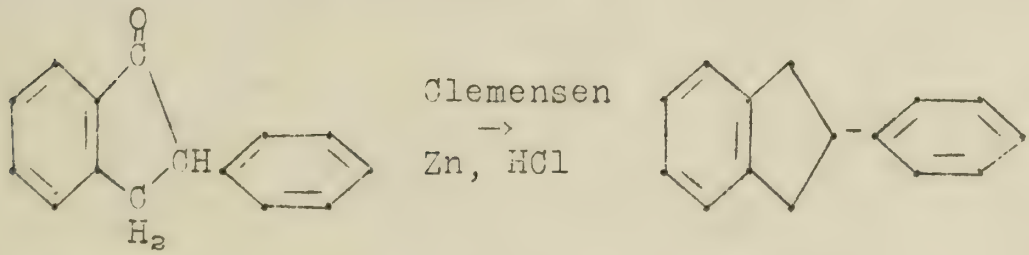




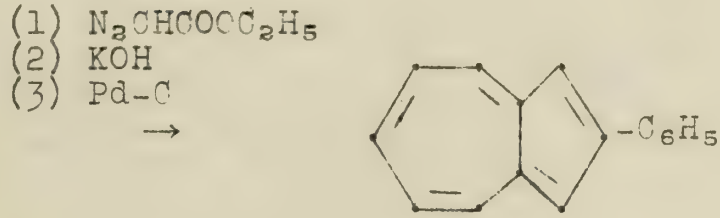
2-n-C_3H_7 Azulene has been prepared by the same way.

(b)

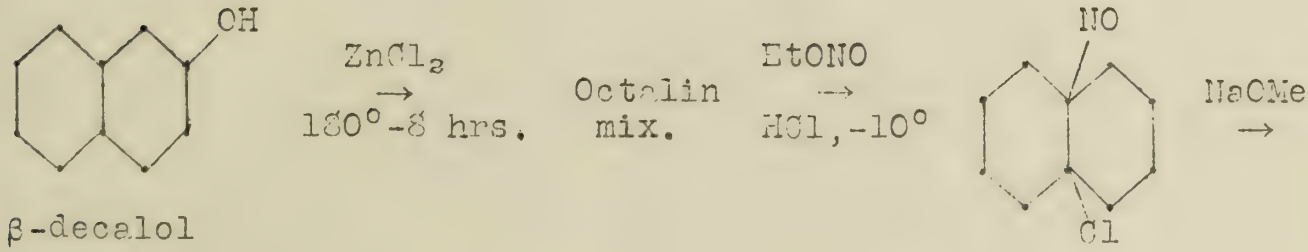




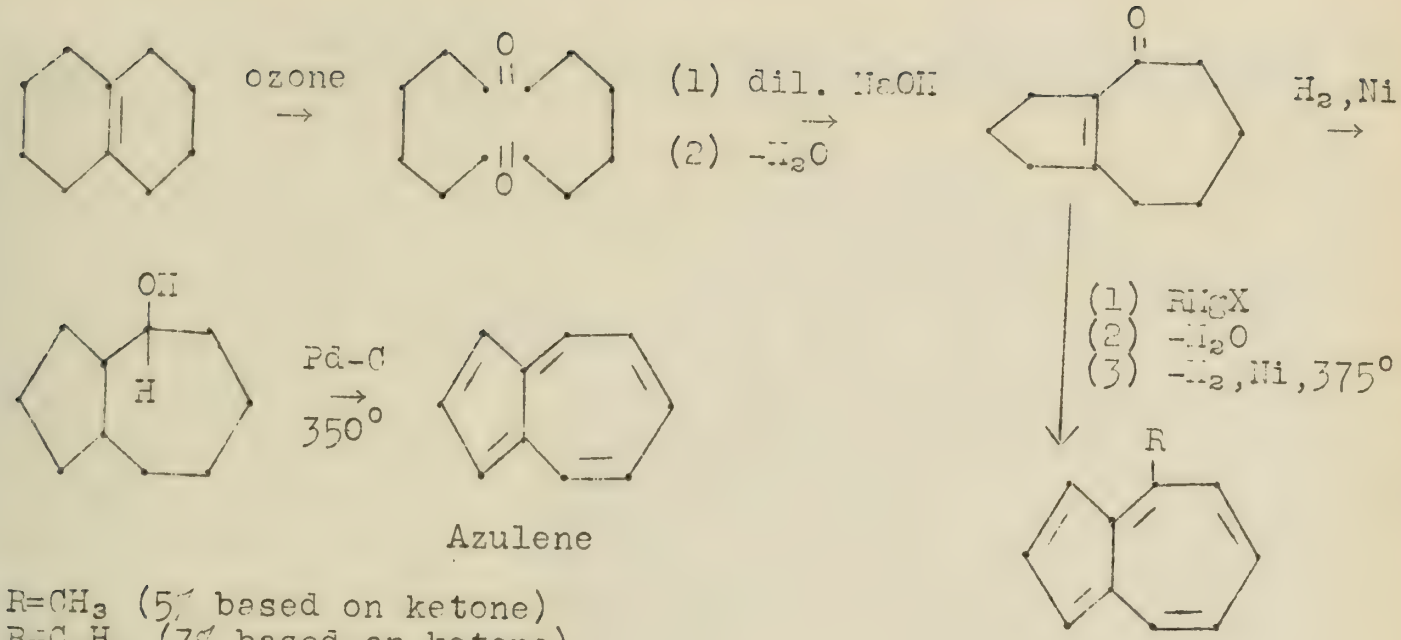
(oil)



3. <u>4-Substituted Azulene</u>.--



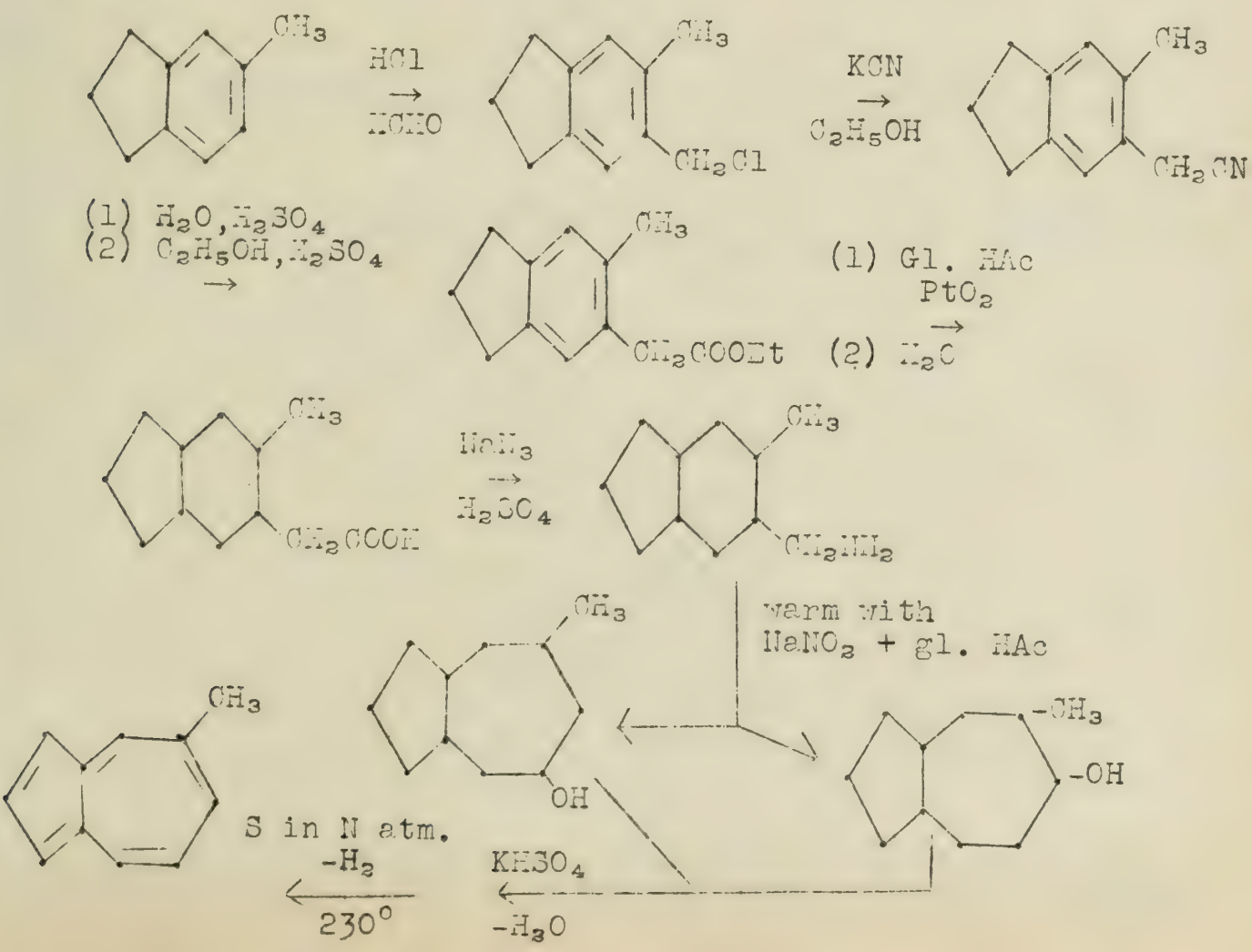
β-decalol



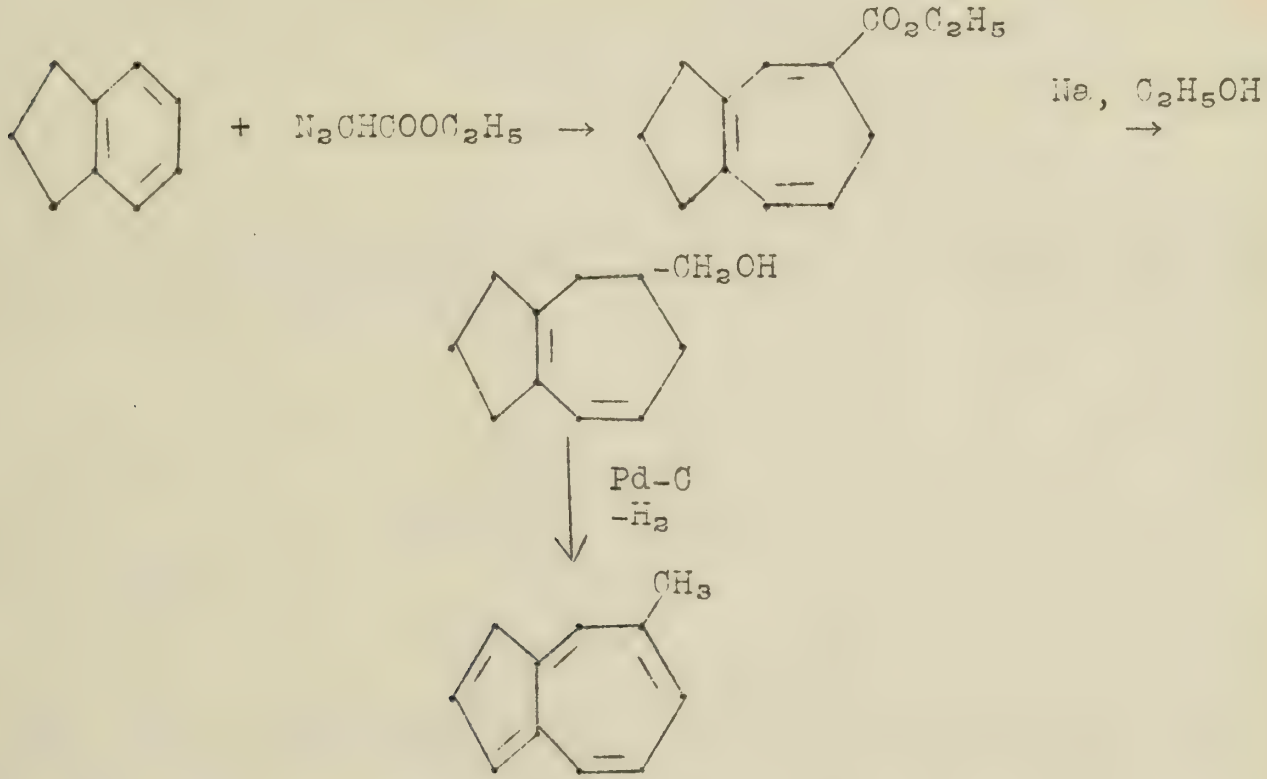
$R=CH_3$ (5% based on ketone)
$R=C_2H_5$ (7% based on ketone)
$R=C_6H_5$ (5% based on ketone)

4. 5-Substituted Azulene.--

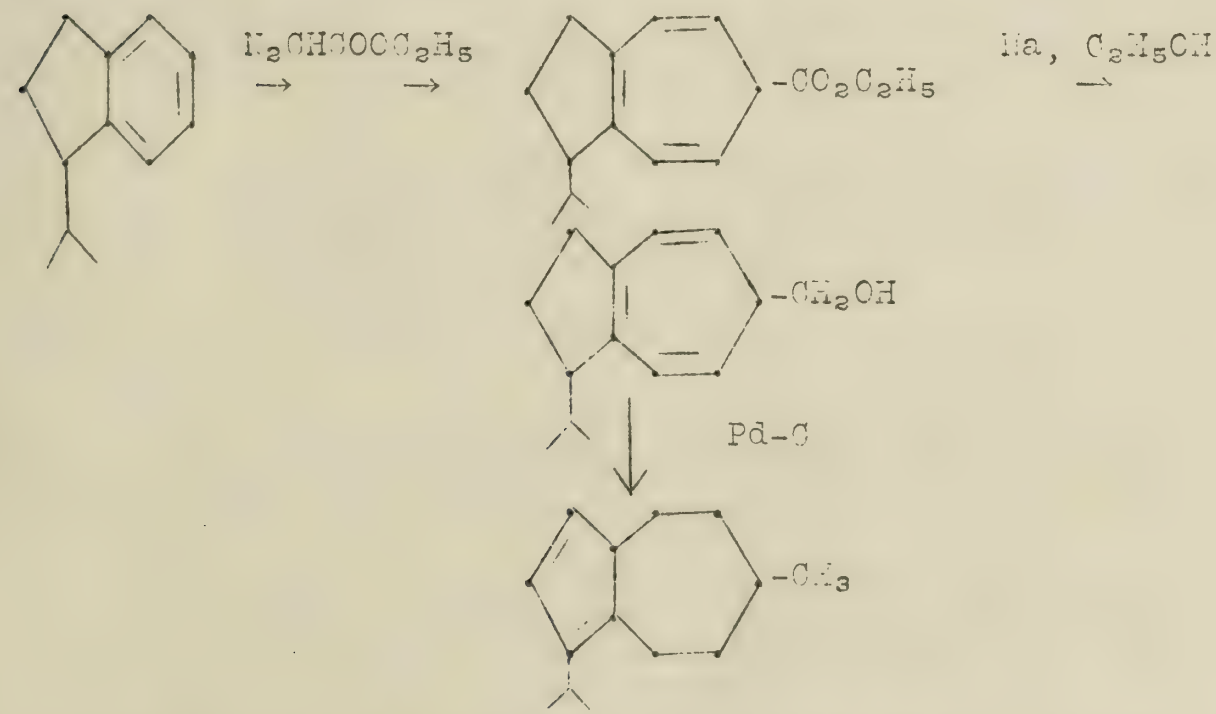
(a) Demjanow's ring enlargement by using HONO on corresponding amines.



In 1943 Arnold succeeded in preparing 5-methyl-azulene by the method shown in 4 (a). In 1947 Arnold prepared 5-methyl-azulene from indane ring, 4 (b).

(b) 

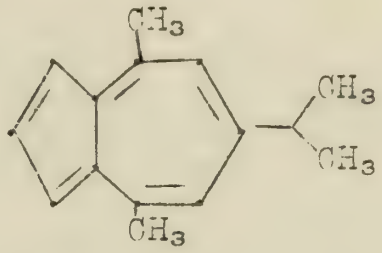
5. <u>6-Substituted Azulene - Prepared by Arnold (1947)</u>.--



By the absorption spectra study it is proved that 6-CH_3-1-isopropylazulene is formed instead of the 5 or 7-CH_3-1-isopropyl

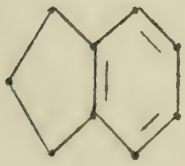
azulene, which would be formed from this reaction if addition occurred at a different point on the benzene ring.

6-Isopropyl-4,8-dimethyl-azulene has been synthesized from 4,7-dimethyl-indane by the above method.

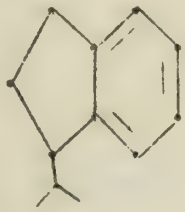


For the synthesis shown above indane, 1-isopropyl-indane and 4,7-dimethyl-indane add the diazoacetic ester as the Kekulé-formulas (A) (B) and (C), respectively.

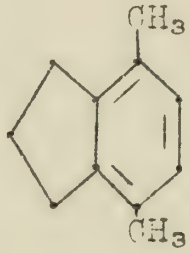
(A)



(B)



(C)



The position and perhaps also the nature of the substitute's in the indane neucleus effect the direction of the addition of diazoacetic ester.

Absorption Spectra Study.--The absorption spectra of aromatic hydrocarbons are known to be influenced by the introduction of alkyl substituents. The absorption bands of azulenes are measured in a Lowe-Schumm spectroscope in hexane solutions. They are divided into three groups, each having very characteristic bands -

Group I. Azulene; 1-methyl azulene; 1,4-dimethyl-azulene; 1,4,7-trimethyl-azulene; 1,4-dimethyl-7-isopropyl-azulene; 4-methyl-azulene; 4,7-dimethyl-azulene.

Group II. 2-methyl-azulene; 2-isopropyl-azulene; 2-isopropyl-4,7-dimethyl-azulene.

Group III. 1,2-dimethyl-azulene; 5-methyl-azulene

The introduction of methyl groups in the 1-position moves the whole band series toward the longer wave length. This is indicated by the difference in coloration. Azulene itself has a definite violet nuance, whereas 1-methyl-azulene has a pure blue tone.

Substitution in the 2-position causes a shift of the main absorption bands to the shorter wave length. The 2-phenyl substituted azulene gives additional strong absorption bands in longer wave length range which might be due to the conjugation of phenyl neucleus with azulene neucleus.

Group III azulenes have no characteristic absorption. The substitution at position 4, 7, 8, etc., also have small effects on the intensity and length of the bands.

In general the 1-substituted azulenes are chiefly blue and the 2-substituted azulenes are mostly violet. It appears that the position rather than the size of the alkyl substitute influences the absorption spectrum of the substituted azulene.

Since the intensity and the wave length of the spectrum are very sharply influenced by different substitutes and substituted positions, the absorption spectra study becomes a chief method for identifying unknown azulenes.

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Reported by Elizabeth H. H. Shen
December 5, 1947

THE SILVER CATALYZED CANNIZZARO REACTION

The Cannizzaro reaction is characteristic of aldehydes which have no hydrogen on the alpha carbon atom. Properly substituted aliphatic aldehydes, aromatic and many heterocyclic aldehydes, and formaldehyde undergo this reaction when treated with base to yield the corresponding alcohols and acids in equal amounts.

In the aromatic series there are certain substituted benzaldehydes which do not undergo this reaction (1). ortho- and para-Hydroxybenzaldehydes, whether further substituted or not, fall into this category. Vanillin is no exception. Recently, Pearl, (2, 3) who was investigating methods of producing vanillic acid, found that when vanillin is treated with silver oxide and excess aqueous sodium hydroxide, vanillic acid is produced in almost quantitative yields even when only a half mole of the oxide is employed. This

$$2\ RCHO + Ag_2O + 2\ NaOH \xrightarrow{NaOH} 2\ RCOONa + 2\ Ag + H_2O + H_2$$

unexpected discovery indicated that silver oxide alone did not accomplish all the oxidation, and that oxygen of the air, and/or sodium hydroxide must have acted as an oxidizing agent. From the observations that vanillin is stable when boiled with sodium hydroxide in air, that this new oxidation reaction also takes place in an inert atmosphere, and that hydrogen is liberated led to the hypothesis that a Cannizzaro reaction had taken place, catalyzed by silver oxide or metallic silver. This was confirmed by using less than a half mole of silver oxide in the reaction, and vanillyl alcohol in the form of its dimer was recovered in the calculated amount depending on the amount of the oxide used.

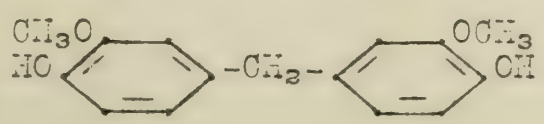
The following equations explain the observed facts.

$$(1)\quad 2\ RCHO + NaOH \xrightarrow{NaOH} RCH_2OH + RCOONa$$

$$(2)\quad \underline{RCH_2OH + Ag_2O + NaOH \rightarrow RCOONa + 2\ Ag + H_2 + H_2O}$$

$$2\ RCHO + Ag_2O + 2\ NaOH \xrightarrow{NaOH} 2\ RCOONa + 2\ Ag + H_2 + H_2O$$

Vanillyl alcohol was never isolated, but its presence was indicated by the formation of its self-condensation product, 4,4'-dihydroxy-3,3'-dimethoxydiphenylmethane. Vanillyl alcohol, alone

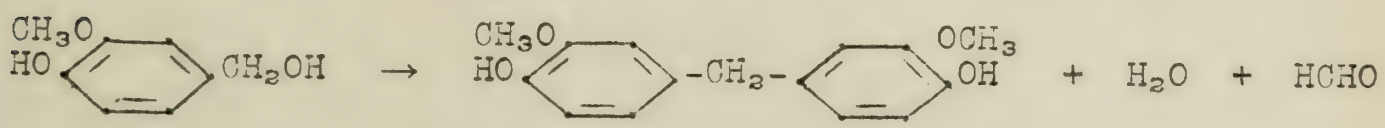


or with vanillic acid, was treated with aqueous sodium hydroxide under conditions simulating the vanillin reaction. In both cases, the same condensation product was obtained, indicating that vanillyl alcohol was formed as the primary product of the Cannizzaro reaction, and that in alkaline solution it reacted to form the bimolecular condensation product. Hydrogen was measured by means of a combustion train, but a quantitative result could not be obtained because of absorption on the silver metal.

Active Silver Metal as the Catalyst.--There were indications that active silver metal formed in the reaction was the catalyst rather than the oxide (5). This was proven by treatment of a solution of vanillin with excess 15% sodium hydroxide in the presence of 100 mol per cent of dry, finely divided silver (from reduction of silver oxide with vanillin and base). A quantitative reaction occurred with formation of equal amounts of vanillic acid and the vanillyl alcohol condensation product.

The catalytic properties of active silver metal prepared from metallurgical silver, heating of silver oxide, reduction of silver nitrate with ferrous sulfate, and vanillic acid (hot and cold) were studied. The hot vanillic acid process was found to be best because it produced active silver metal of greater surface area than the others. This catalyst was found to be stable, and could be used repeatedly, as in a continuous flow process.

The Crossed Cannizzaro Reaction.--The crossed Cannizzaro reaction of vanillin and formaldehyde (mole ratio 1:1) was found to occur in the presence of silver catalyst and excess sodium hydroxide to form the condensation product of vanillyl alcohol and no acid. However, when the formaldehyde-vanillin ratio was 5:1, a yield of 82.5% of vanillyl alcohol was obtained. Apparently the self-condensation of vanillyl alcohol is repressed by the excess formaldehyde. All attempts to effect Cannizzaro reactions



with aldehydes of this type in the absence of silver catalyst failed completely.

Application of the silver Catalyzed Reaction to other Aldehydes.--Several aldehydes which under ordinary conditions fail to undergo the Cannizzaro reaction were studied to determine whether the silver catalyzed reaction of vanillin was applicable to them (6).

(1) o-Vanillin (2-hydroxy-3-methoxybenzaldehyde) with 0.5 mole of silver oxide and excess alkali gave almost quantitative yields of o-vanillic acid.

(2) 5-Chlorovanillin was easily oxidized to the acid with 0.5 mole of silver oxide. When the oxide-vanillin ratio was reduced, 5-chlorovanillyl alcohol appeared in theoretical amounts calculated on the basis of the Cannizzaro reaction. The reaction with active silver and excess alkali gave equivalent amounts of the acid and alcohol, and the crossed Cannizzaro reaction with formaldehyde yielded only 5-chlorovanillyl alcohol.

(3) Salicylaldehyde reacted in the same manner as 5-chlorovanillin. Both aldehydes yielded the alcohols in contrast to vanillin which yielded the condensation product of the alcohol.

(4) p-Hydroxybenzaldehyde was easily oxidized by 0.5 mole of silver oxide and excess alkali to the acid, and underwent the regular and crossed Cannizzaro reactions in the presence of active silver. Either crystalline or resinous p-hydroxybenzyl alcohol was obtained, depending upon the experimental procedure.

(5) Dismutation of p-dimethylaminobenzaldehyde by the Cannizzaro reaction took place with ease in the presence of active silver to yield equivalent amounts of p-dimethylaminobenzoic acid and p-dimethylaminobenzyl alcohol.

All the above reactions were repeated without catalytic silver, and in no case did reactions take place.

Although only one aminobenzaldehyde was studied, the series of reactions cited indicate that the active silver catalyzes the Cannizzaro reaction of all ortho- and para-hydroxybenzaldehydes, amino and substituted aminobenzaldehydes, none of which undergoes the reaction in the presence of alkali alone.

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Reported by William E. Hamlin
December 5, 1947

INTRODUCTION OF ISOTOPIC CARBON INTO ORGANIC COMPOUNDS

Introduction.--Natural carbon has two isotopes with mass numbers 12 and 13, the latter having an abundance of 1.10 atom per cent. Radioactive isotopes were found with mass numbers 10, 11, and 14. Isotopes C^{11}, C^{13} and C^{14} have been used as tracer elements.

Carbon-13 is commercially available in the form of $NaC^{13}N$ and $NaHC^{13}O_3$ (2,3). Unfortunately, use of C^{13} is predicated on the availability of a mass spectrometer for its analysis. In general, radioactive isotopes are preferred as tracers, since their methods of detection are relatively simple in high dilution.

Carbon-11 is prepared chiefly by the bombardment of B^{10} with deuterons in a cyclotron. The use of C^{11} as a tracer is limited by its relatively short half-life, 20.35 $\pm$ 0.08 minutes, and its scarcity. C^{11} has definite advantages as a tracer isotope. It gives off gamma rays, and therefore is easy to detect with a Geiger-Müller counter. This property makes it particularly advantageous as a tracer isotope for experiments of short duration requiring high dilution. The gamma radiation of this isotope makes the tracing of C^{11} possible in an intact organism.

Carbon-14 results from the reaction of slow neutrons with nitrogen. The advent of the chain-reacting piles with their

$$_7N^{14} + {}_0n^1 \rightarrow {}_6C^{14} + {}_1H^1$$

abundance of slow neutrons has made it possible to produce C^{14} on a commercial scale. The ease of production of C^{14}, as well as its long half-life - 4700 years (4), makes it the best tracer isotope of carbon.

The principal difficulty in its use has been the assay of compounds containing C^{14}. The low-energy β-ray emission of C^{14} is difficult to count. With present Geiger-Müller counters, liquids containing C^{14} cannot be assayed, and the assay of solids involves considerable error. The best assay method (5) has been the conversion of the carbon compound to CO_2 and analysis of the gas in the counter. Newly developed counters and electroscopes may soon eliminate this difficulty in assay.

Applications.--The carbon isotopes have numerous applications in chemical research. Compounds containing labeled atoms may be used in medical research, intermediary metabolism studies, analyses by isotope dilution, biological studies, determination of rates of biochemical reactions, and in the study of the mechanism of organic reactions.

An example of this latter application is the recent work of Neville and Brown (6) on the rearrangements of unsymmetrical α-

diketones. Sodium hydroxide treatment of phenylglyoxal labeled in the α-position with C^{14} yielded mandelic acid labeled in the α-position. This demonstrates that no rearrangement of the carbon skeleton occurs.

$$CH_3C^*OOH \xrightarrow[AlCl_3]{C_6H_6} C_6H_5C^*OCH_3 \xrightarrow{SeO_2} C_6H_5C^*OCHO \xrightarrow{NaOH} C_6H_5C^*HOHCOOH$$

Other examples of the use of carbon isotopes in the study of mechanisms are the thermal decarbonylation of pyruvic acid (7), the Willgerodt reaction (8,9), and the Arndt-Eistert synthesis (10).

Starting Materials.--The synthesis of complex compounds is dependent upon the successful preparation of starting material from barium carbonate. Recently much work has been done to prepare simple molecules in high yield from $C^{14}O_2$. These reactions are also applicable to $C^{11}O_2$ and $C^{13}O_2$.

	% Yield
Sodium Cyanide (11):	
$BaC^*O_3 + NaN_3 \xrightarrow[\text{atm.}]{N_2} NaC^*N$	75-80
Hydrogen Cyanide (12):	
$C^*O_2 + NH_3 \xrightarrow[620^\circ]{\text{K mirror}} HC^*N$	90-96
Acetylene (13):	
$Ba + C^*O_2 \xrightarrow[\text{5-10 min.}]{600^\circ} BaC_2^* \xrightarrow{H_2O} HC^*\equiv C^*H$	90-98
Methanol and Methyl Iodide (14):	
$C^*O_2 + 3H_2 \xrightarrow[KCuAl_2O_3]{\text{460 atm.}} C^*H_3OH + H_2O$	80-90
$C^*H_3OH + I_2 + P_4 \rightarrow C^*H_3I$	95-100
Acetic Acid (15):	
$CH_3MgI + C^*O_2 \rightarrow CH_3C^*OOMgI \rightarrow CH_3C^*OOH$	70

In order to obtain good yields of the acid by the Grignard

reaction, the carbonation and hydrolysis must be conducted as rapidly as possible (5 to 6 minutes), since an excess of carbon dioxide is not used.

C^{14}-labeled compounds other than $BaC^{14}O_3$ are being prepared by several laboratories of the Atomic Energy Commission. C^{14}-labeled methanol, barium carbide, and sodium formate are currently available in small quantities for laboratories outside the Commission. Additional C^{14}-labeled compounds, useful largely as intermediates, are expected to become available soon (16).

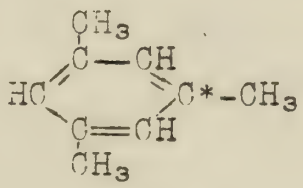
Syntheses.--The following reactions demonstrate how carbon isotopes can be introduced into complex organic molecules.

Mesitylene (17):

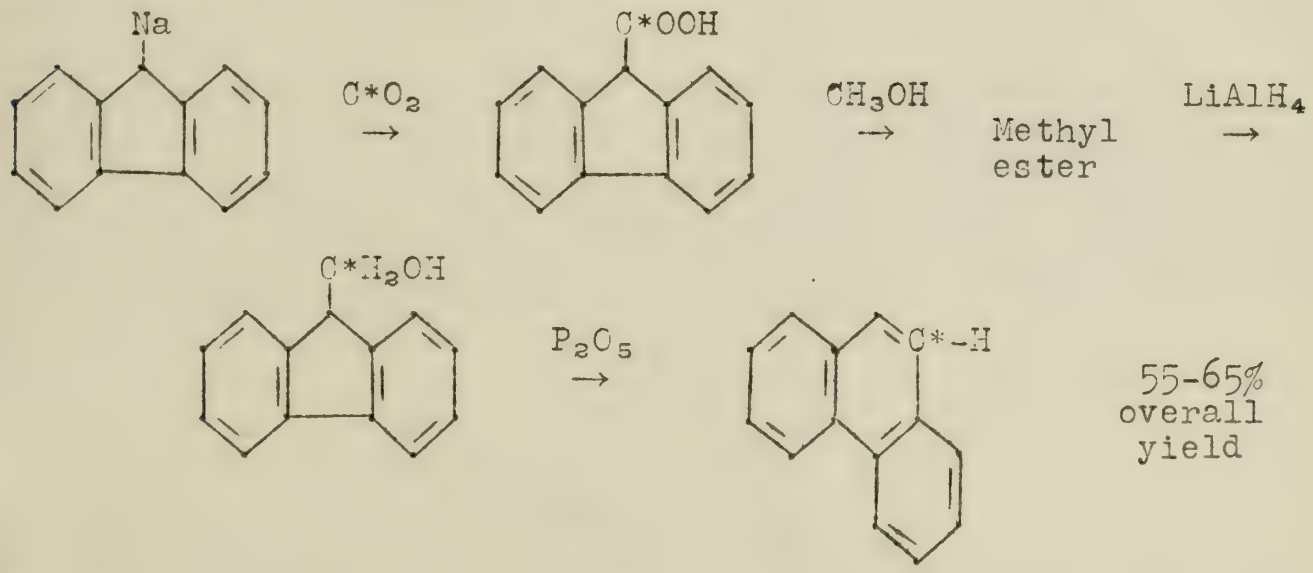
$$CH_3C^*OOH \xrightarrow{Ba(OH_2)} Ba(C^*OOCH_3)_2 \xrightarrow[500^\circ]{\text{vacuum}} CH_3C^*OCH_3 + BaC^*O_3$$

(89% yield)

$$CH_3C^*OCH_3 + 2CH_3COCH_3 \xrightarrow{H_2SO_4}$$



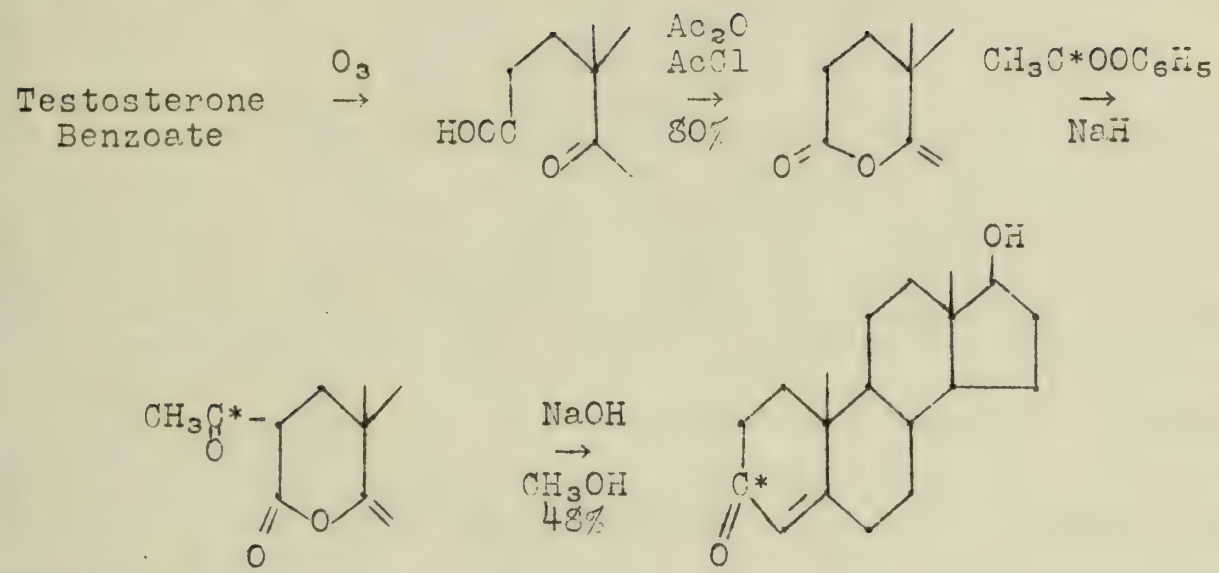
Phenanthrene-9-C^{14} (18):



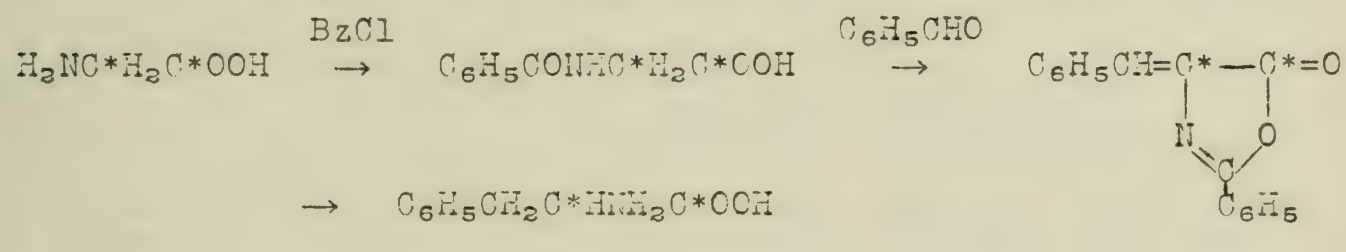
Nicotinic Acid (20):

Carbonation with C^*O_2 of the Li compound formed from β-bromopyridine and n-butyl lithium gave a 70% yield of nicotinic acid.

Testosterone (21):



Phenylalanine (22):



In addition, syntheses have recently been published for labeled β-dimethylaminoethyl benzhydryl ether hydrochloride (Benadryl hydrochloride) (23), $CH_3C^*OC^*OOH$ (24), $CH_3C^*OCH_2C^*OOH$ (24), $CH_3C^*OCH_2CCOH$ (24), $CH_3COCH_2C^*COH$ (24), $C^*H_3SCH_2CH_2CHNH_2COOH$ (25), lauric acid-1-C* (26), dodecylamine-1-C* (26), tyrosine-3-C* (27), cholesterone (28), ethyl carbamate (29), p-aminobenzoic acid (20), and 1,2,5,6-dibenzanthracene-9-C* (19).

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Reported by H. L. Jackson
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RECENT WORK ON THE REACTIONS OF CARBON MONOXIDE

Considerable quantities of carbon monoxide are employed in the methanol and acetic acid syntheses, and in the Fischer-Tropsch process, but these processes require very high pressures and temperatures. In 1924 Fischer and Tropsch (1) reported that by passing carbon monoxide and hydrogen over a catalyst of iron filings treated with potassium carbonate, at 400-450°C. and 150 atm., they obtained a complex mixture of acids, alcohols, aldehydes, and ketones. Since that time many new catalysts and variations of the process have been developed, so that either olefins or oxygenated compounds may be the principal product. Starting in about 1935 the research on carbon monoxide was considerably increased, particularly in the United States and Germany. Two decidedly different paths of experimentation were developed. In the United States the investigations concerned high temperatures (300-400°C.) and pressures ($\rightarrow$ 700 atm.), and employed catalysts such as aluminum chloride, phosphoric acid, metal oxides or activated charcoal. In Germany less strenuous conditions were employed (25-200°C., 3-100 atm.), and the catalysts were nickel or iron carbonyls, or nickel salts (2, 3).

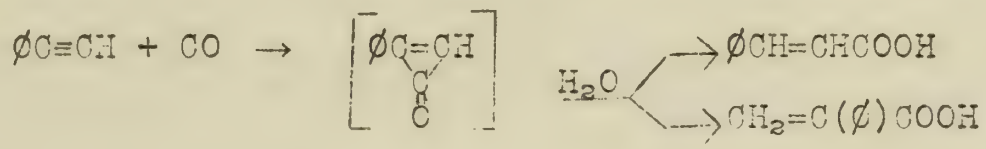
Reaction With Acetylenes.--Many derivatives of acrylic acid can be prepared from acetylenes, carbon monoxide and some compound containing an active hydrogen. The reactions may be carried out using the stoichiometric amount of nickel carbonyl, or catalytically by passing the carbon monoxide over metals or metal salts which can form carbonyls. The general equation for the reaction is as follows. Both batch and continuous processes for the preparation of

$$C_2H_2 + ROH + 1/4\ Ni(CO)_4 + 1/2\ HCl\ aq. \rightarrow CH_2{=}CHCOOR + 1/4\ NiCl_2\ aq. + 1/4\ H_2$$

ethyl acrylate have been developed. The former takes place at 40°C. and atmospheric pressure, using nickel carbonyl; the latter at 150-180°C. and 30 atm., using nickel bromide as catalyst. Other derivatives may be made up substituting amines, mercaptans, acids, etc., for the alcohol in the above equation. It is stated, without being specific, that the reaction has also been extended to other acetylenic compounds such as methyl-, ethyl-, phenyl-, or divinylacetylene, alkinols and alkindiols and their ethers and esters, and also to acetylenes with amino or mercaptan groups attached. The yields in the reactions are very high, and in many cases are quantitative.

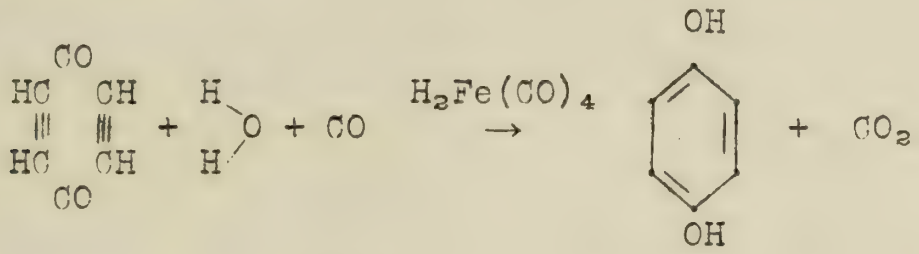
The most satisfactory mechanism proposed so far is the formation of cyclopropenone as the intermediate, which on fission would lead to the acrylate derivatives. By this mechanism the formation

of either cinnamic acid or α-phenylacrylic acid might be expected from phenylacetylene. Actually the latter is the only product.

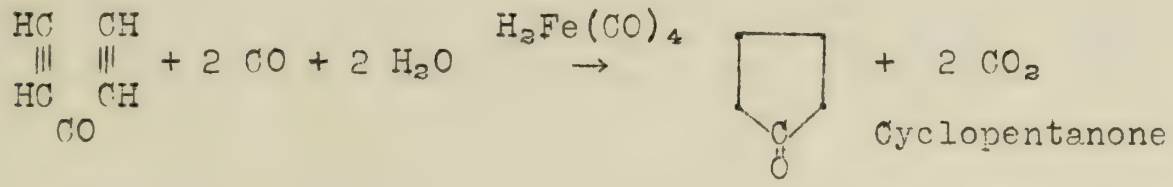


Similarly, with phenylmethylacetylene, fission of the hypothetical phenylmethylcyclopropenone would lead to α-phenylcrotonic acid and α-methylcinnamic acid. In this case both are obtained.

When carbon monoxide and acetylene are reacted in the presence of iron hydrocarbonyl, or iron pentacarbonyl plus a base, the products are considerably different. From acetylene itself hydroquinone is formed in 20-30% yield. Other examples such as cyclo-

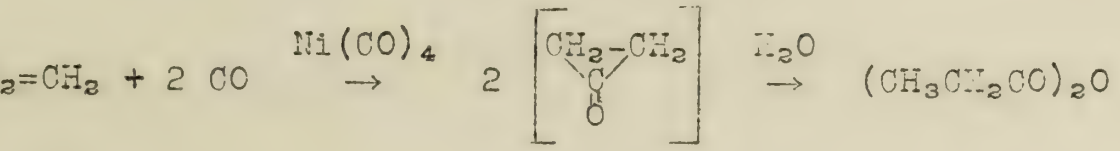


pentanone and hydrindone have been reported. It is stated that



this type of reaction is applicable to substituted acetylenes, ethers of acetylenic alcohols, and dimethylaminoacetylenes.

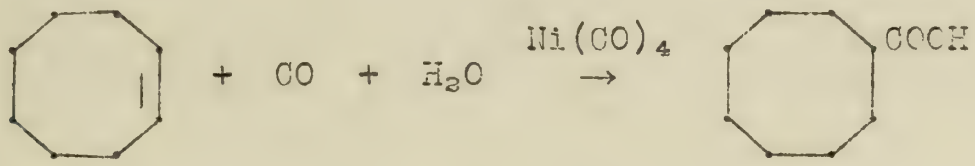
Reaction With Olefins.--The reaction between olefins and carbon monoxide was run at 200-300°C. and 150-300 atm., and was applied to olefins having from one to twenty-five carbons. Thus, from ethylene, propionic anhydride may be prepared. The C_{12}-C_{18} olefins



were converted to the acids, which were then hydrogenated to the alcohols to be used for detergents. The alcohols could also be

obtained by hydrogenating the aldehydes prepared by the Oxo synthesis, in which an olefin and carbon monoxide were passed over cobalt-thoria on kieselguhr at 125°C. and 200 atm. (2, 4).

Cyclic olefins behave in the normal manner, giving the carboxylic acid or its derivative. When butadiene is used, it first



dimerizes to vinylcyclohexene, which then reacts further at the double bonds to give a variety of products. Carpenter (5) has obtained propionic acid from ethylene, using as catalyst phosphoric acid on charcoal. Other catalysts patented for the preparation of acids and esters are active charcoal and oxides of Ti, Al, Si, W, Cr (6). Perhaps most unusual is the reaction reported by Hanford (7).

$$CH_2{=}CH_2 + CO \xrightarrow[(\emptyset CO)_2O_3]{BF_3 \cdot H_2O} (C_2H_5)_2(CH_3)CCOOC_2H_5$$

Unsaturated alcohols and acids have also been made to undergo addition of carbon monoxide, again using nickel carbonyl as catalyst. Methacrylic acid has been made from allyl alcohol by the dehydration of the intermediate β-hydroxyisobutyric acid.

$$CH_2{=}CHCH_2OH + CO + H_2O \rightarrow CH_3\underset{CH_2OH}{C}HCOOH \xrightarrow{-H_2O} CH_2{=}\underset{CH_3}{C}COOH$$

Similarly butene-1-ol-4 yields a mixture of δ-valerolactone and methylbutyrolactone. Other examples are the preparation of dicarboxylic acids from such unsaturated acids as oleic, undecylenic, etc. The product is usually a mixture since the carbonyl group may appear at either end of the double bond.

$$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH \xrightarrow{CO + H_2O} HOOCCH(C_8H_{17})(CH_2)_8COOH$$

oleic acid — α-octylnonanedicarboxylic acid and its isomer, α-nonylsebacic acid

When olefins and carbon monoxide are reacted over iron hydrocarbonyl the principal products are alcohols. Thus ethylene gave n-propanol, together with small amounts of acids and higher alcohols.

Reaction With Paraffins.--The first data on the reaction of carbon monoxide and paraffins were reported by Hopff (8), who used aluminum chloride as catalyst and reaction conditions of 20-50°C. and 100-150 atm. Hopff stated that the reaction would not go with hydrocarbons below butane, but Ipatieff (9) has recently reported the reaction of propane. The main products obtained are summarized as follows:

Propane gives $(CH_3)_2CHCOOH$, $(CH_3)_2CH\overset{O}{\overset{\|}{C}}OCH_2CH(CH_3)_2$, and $(CH_3)_2CH\overset{O}{\overset{\|}{C}}CH{=}C(CH_3)_2$; n-butane gives $CH_3\overset{O}{\overset{\|}{C}}CH(CH_3)_2$, $C_2H_5CH(CH_3)COOH$, n-$C_4H_9\overset{O}{\overset{\|}{C}}CH_2CH(CH_3)_2$; i-butane gives $CH_3\overset{O}{\overset{\|}{C}}CH(CH_3)_2$, $(CH_3)_3CCOOH$, and $(CH_3)_3C\overset{O}{\overset{\|}{C}}CH_2CH(CH_3)_2$; n- and i-pentane gives $(CH_3)_2CH\overset{O}{\overset{\|}{C}}C_2H_5$, $C_3H_7CH(CH_3)COOH$; n-hexane gives $C_3H_7\overset{O}{\overset{\|}{C}}CH(CH_3)_2$ plus unidentified acids.

The exact mechanism of these reactions has not been fully demonstrated, although the isomerizing action of aluminum chloride is well known. Hydrogen chloride is usually present in reactions with paraffins, and one mechanism proposed goes according to the following series of reactions. The products are

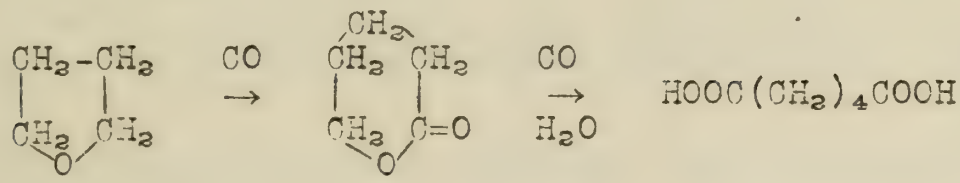
$$(CH_3)_2CHCH_3 \xrightarrow[AlCl_3]{-H_2} (CH_3)_2C{=}CH_2 \xrightarrow[CO]{HCl} (CH_3)_2C(CHO)CH_2Cl \xrightarrow[-HCl]{H_2}$$

$$(CH_3)_3CCHO \xrightarrow{AlCl_3} (CH_3)_2CH\overset{O}{\overset{\|}{C}}CH_3$$

not entirely the result of rearrangement, as is shown in the formation of n-butylisobutyl ketone from n-butane. Hopff found that aluminum chloride, hydrogen chloride and carbon monoxide form a stable adduct under his reaction conditions, and assumes that this is the reacting form of carbon monoxide.

Miscellaneous Reactions.--Aliphatic and cyclic ethers may react with metal carbonyls to produce acids, but a small amount of halogen is required to promote the reaction. Adipic acid may be

produced from tetrahydrofuran in the following manner. A small



amount of valeric acid is formed as a by-product, but the reaction may be controlled to give the δ-valerolactone as the main product. Tetrahydropyran, when treated in the same manner, yields pimelic acid. There are many examples in the literature for the formation of acids from alcohols and carbon monoxide, usually with an acid-type catalyst (10). Hardy (11) considers that these reactions proceed by the dehydration of the alcohol to an olefin, which then reacts to form the acid. Theobald (12) has reported that trichloroacetyl chloride is formed in good yield when carbon tetrachloride and carbon monoxide are passed over aluminum chloride at 200°C. and 95 atm.

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Reported by C. H. Young
December 5, 1947

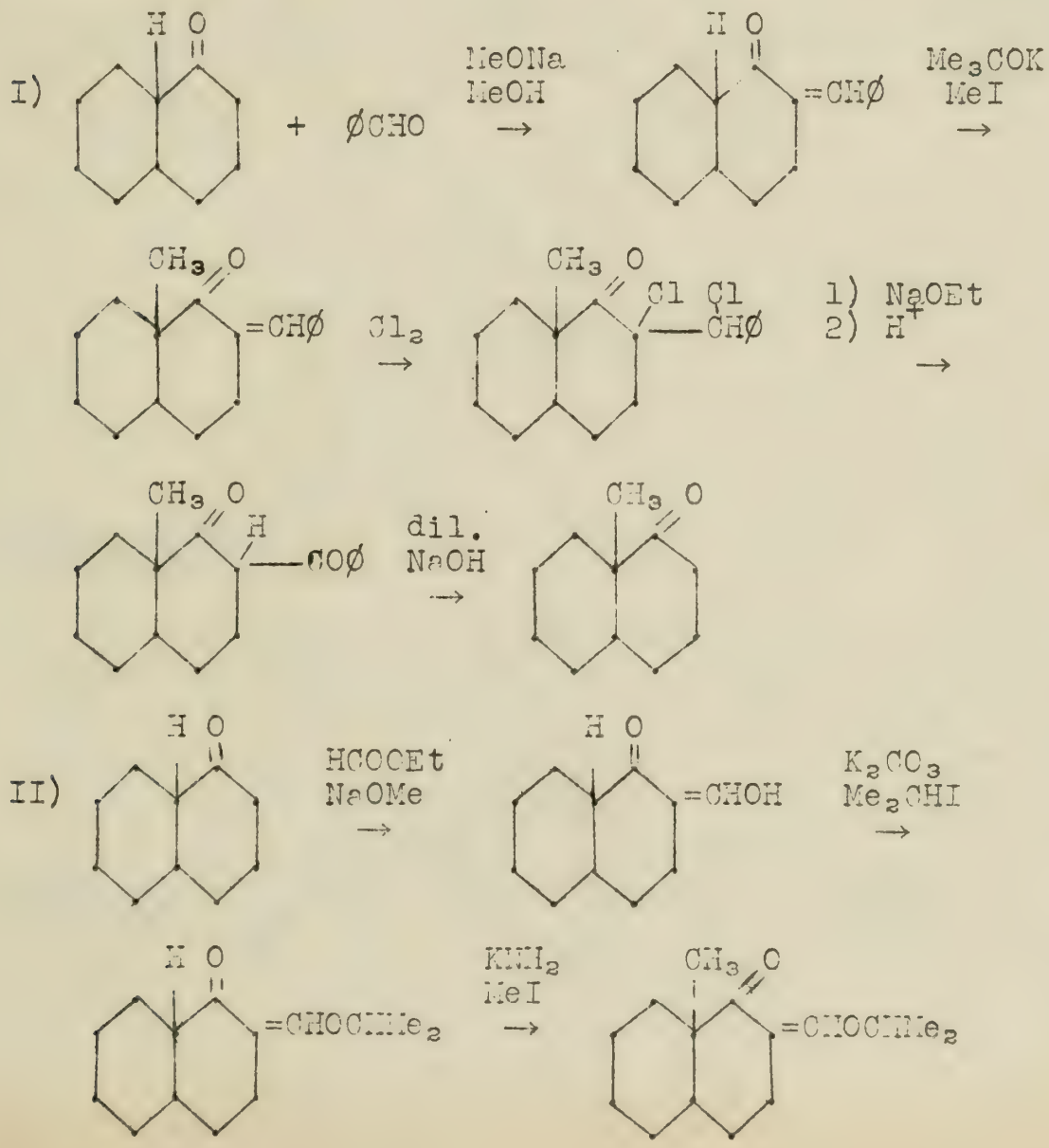
SYNTHESES OF ANGULAR METHYL GROUPS

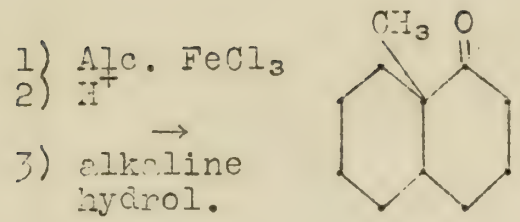
Sterols and related compounds contain angular methyl groups. Workers in this field have devoted a great deal of time developing new and better syntheses for this group. The purpose of this seminar is to discuss the syntheses now available and their merits and defects.

The works of Linstead, Robinson, and Woodward have been reported previously (1).

(A) Bachmann: (2)

(B) Johnson: (3-5)





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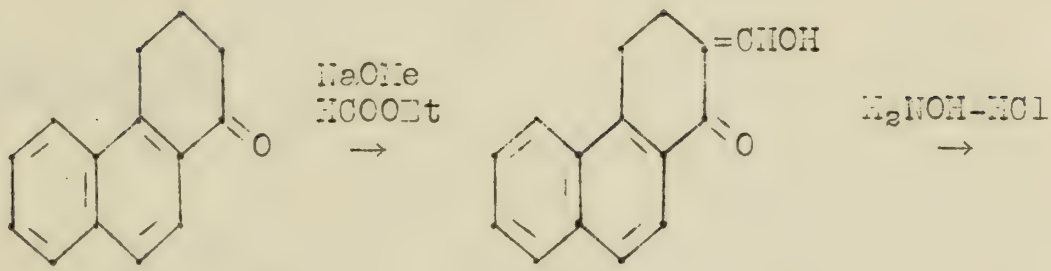
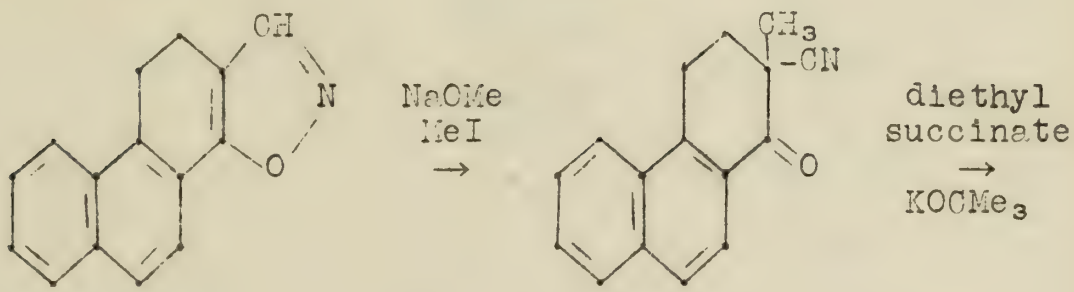
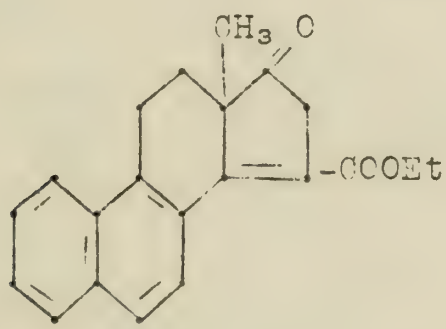
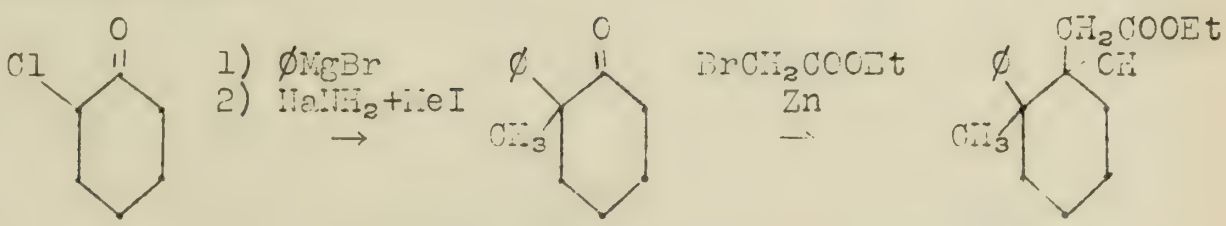
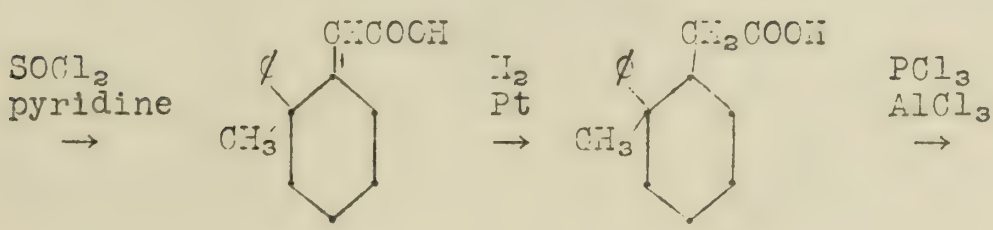


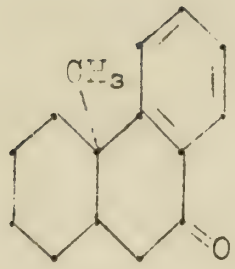




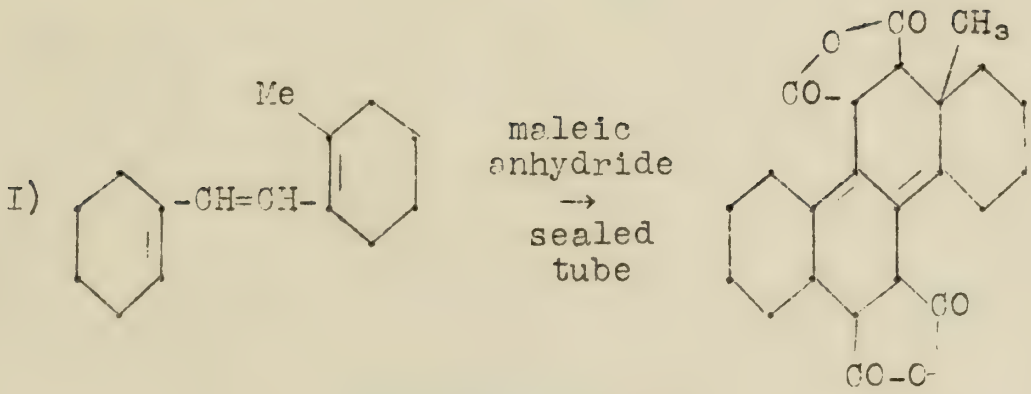
(C) <u>Newman: (6-7)</u>



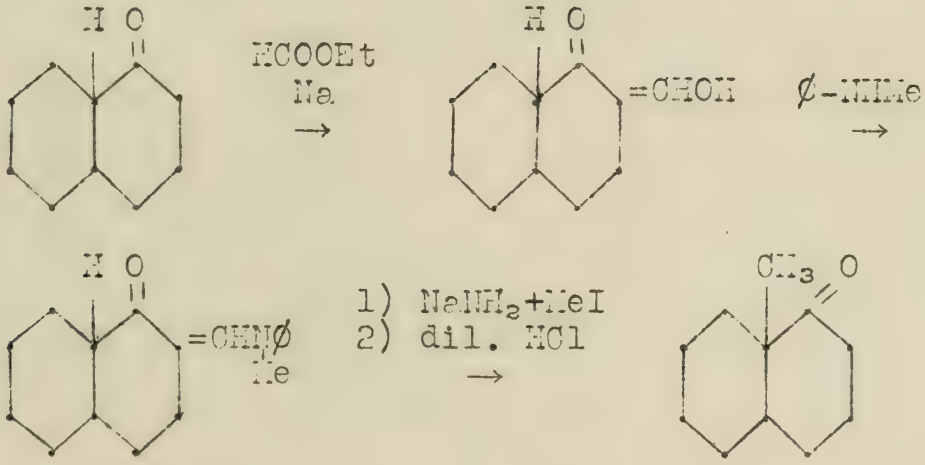




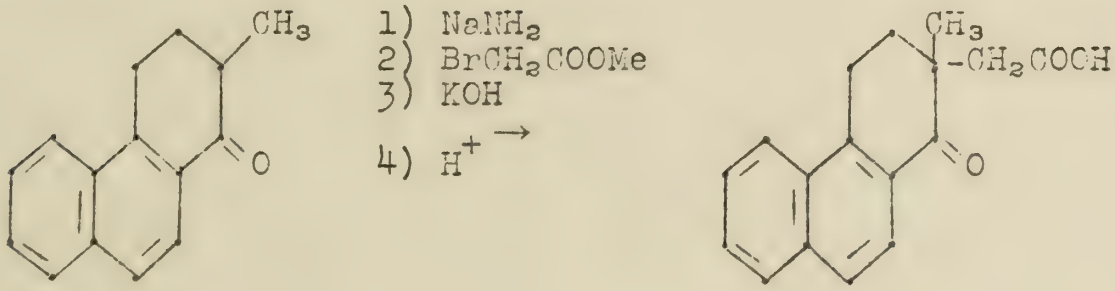
(D) Butz: (8-10)

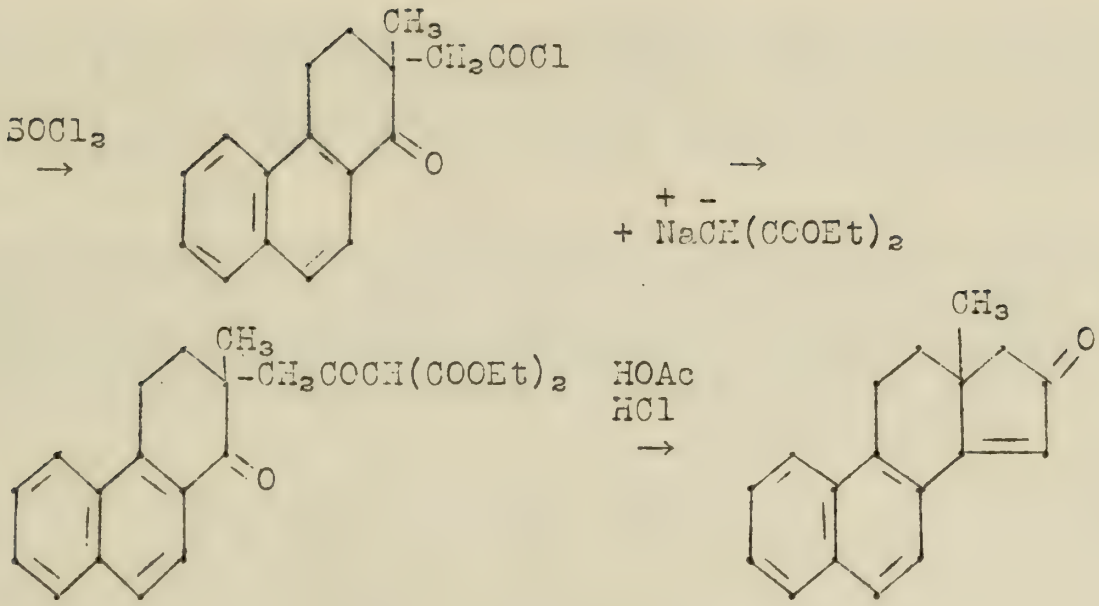


(E) Robinson: (11)



(F) Wilds: (12)





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Reported by John P. Pellegrini
December 12, 1947

FREE RADICAL MECHANISM OF VINYL POLYMERIZATION

Recent extensive theoretical treatments and accumulated experimental data of addition polymerization of vinyl compounds initiated by free radicals have established a generally accepted reaction mechanism. Such a free radical chain mechanism is summarized in this paper.

A. Initiation.--Free radical type polymerization is initiated by conditions or reagents which produce free radicals. Many studies have been focused on thermal or photochemical activation and particularly acid peroxide initiations (1,2,3). Thermal initiation appears to be a bimolecular activation (4,5,6).

$$2\ \underset{\emptyset}{CH}{=}CH_2 \rightarrow \cdot\underset{\emptyset}{CH}CH_2CH_2\underset{\emptyset}{CH}\cdot \qquad (1a)$$

$$2\ M \rightarrow 2\ M\cdot \qquad (1b)$$

The peroxide initiation is an unimolecular scission.

$$R\overset{O}{\overset{\|}{C}}OO\overset{O}{\overset{\|}{C}}R \rightarrow 2\ R\overset{O}{\overset{\|}{C}}O \qquad (2a)$$

$$R\overset{O}{\overset{\|}{C}}O\cdot \rightarrow R\cdot + CO_2 \qquad (2b)$$

R=Ø, p-Br-Ø, p-Cl-Ø, CH_3, $ClCH_2$, p-CH_3OØ, 3,4,5-tri BrØ,

The extent of decarboxylation increases with increase in temperature and dilution. If a reaction solvent is used, hydrocarbons, acids and esters are isolated due to the reaction of solvent with the free radicals generated (3).

$$\emptyset CO_2\cdot + RH \rightarrow \emptyset H + CO_2 + R\cdot$$

$$\emptyset CO_2\cdot + RH \rightarrow \emptyset CO_2H + R\cdot$$

$$R\cdot + (\emptyset CO_2)_2 \rightarrow \emptyset CO_2R + \emptyset CO_2\cdot$$

B. Propagation.--

$$R\cdot + M \rightarrow RM\cdot \qquad (3a)$$

$$RM\cdot + M \rightarrow R(M)_2\cdot \qquad (3b)$$

$$R(M)_n\cdot + M \rightarrow R(M)_{n+1}\cdot \qquad (3c)$$

The propagation step follows second-order kinetics and the molecular weight of the polymer is inversely proportional to the square root of initiator concentration (7). Both aryl and aryl carboxylic acid fragments have been found in the polymer molecules. Many found one "catalyst" fragment per polymer molecule (1); few found one to three such fragments (8). The presence and the amount of "catalyst" fragments can be determined by chemical method, spectroscopic absorption and radioactivity of a suitable substituent (2,8,9).

A closer examination of the addition of a free radical to a double bond shows that the following two possibilities can occur.

$$R\cdot + CH_2{=}\underset{X}{\underset{|}{C}}H \rightarrow RCH_2{-}\underset{X}{\underset{|}{C}}H\cdot \qquad (4a)$$

$$R\cdot + \underset{X}{\underset{|}{C}}H{=}CH_2 \rightarrow R\underset{X}{\underset{|}{C}}H{-}CH_2\cdot \qquad (4b)$$

The product in (4a) generally has more resonance stabilization than that in (4b) owing to the presence of the substituent on the free-radical carbon atom.

Thus the successive additions in the same manner explain the observed predominance of head-to-tail vinyl polymers. However, we expect that a minor percentage of head-to-head tail-to-tail structures should also occur, particularly in those instances where resonance stabilization is small, e.g. when X=Cl or $OCOCH_3$. Leutner and Hory found 2% 1,2-glycol in polyvinyl alcohol which was obtained from hydrolysis of polyvinylacetate (10).

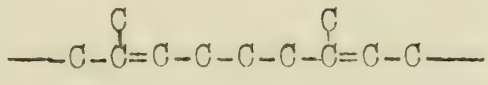
In case of polymers of dienes as isoprene, the problem is complicated by a simultaneous occurrence of 1,2 (or 3,4) as well as 1,4-addition.

$$R\cdot + \underset{\uparrow}{C}{=}\overset{C}{\overset{|}{C}}{-}C{=}C \rightarrow \begin{cases} R{-}C{-}\overset{C}{\overset{|}{C}}{=}C{-}C\cdot & (5a) \\ \quad \downarrow\uparrow & \\ R{-}C{-}\underset{\cdot}{\overset{C}{\overset{|}{C}}}{-}C{=}C & (5b) \end{cases}$$

$$R\cdot + C{=}\overset{C}{\overset{|}{C}}{-}C{=}\underset{\uparrow}{C} \rightarrow \begin{cases} R{-}C{-}C{=}\overset{C}{\overset{|}{C}}{-}C\cdot & (6a) \\ \quad \downarrow\uparrow & \\ R{-}C{-}\underset{\cdot}{C}{-}\overset{C}{\overset{|}{C}}{=}C & (6b) \end{cases}$$

Addition of R· to carbons 2 and 3 are extremely unlikely due to absence of resonance. Since thermally polymerized isoprene was

found to have preponderantly the following head-to-tail structures,



this structure shows one of the reactions 5 and 6 occurs in marked preference to the other. Ozonolysis offers no clue as to which is the preferred one. However, available evidence by infrared spectroscopy study favors reaction (6).

C. Chain Transfer.--Chain transfer proceeds in either of the following two ways, where Y-Z may be a monomer, a solvent molecule, a foreign reagent or a previously formed polymer molecule (5,11, 12).

$$R(M)_n\text{-}CH_2CHX\cdot \rightarrow R(M)_n\text{-}CH{=}CHX + H\cdot \qquad (7a)$$

$$R(M)_n\text{-}CH_2CHX\cdot + Y\text{-}Z \rightarrow R(M)_n\text{-}CH_2\underset{Y}{C}HX + Z\cdot \qquad (7b)$$

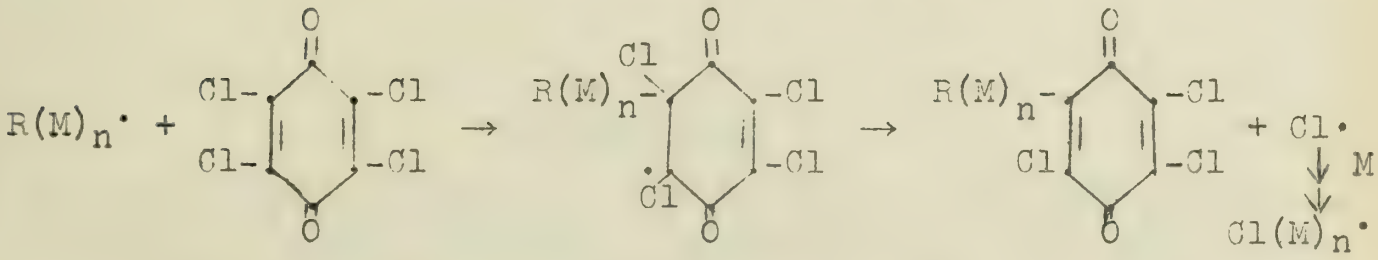
$$H\cdot + M \rightarrow\rightarrow H(M)_n\cdot \quad Z\cdot + M \rightarrow\rightarrow Z(M)_n\cdot \qquad (7c)$$

Chain transfers with a monomer, a solvent molecule, a foreign reagent and a polymer molecule are illustrated respectively by the following reactions.

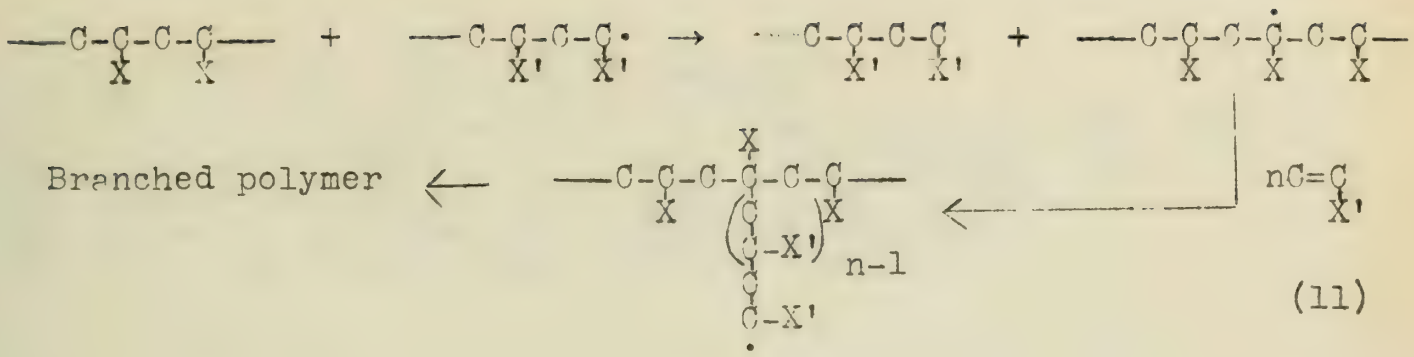
$$RCH_2\text{-}\underset{\cdot}{C}H\emptyset + CH_2{=}CH\text{-}\emptyset\cdot \rightarrow RCH_2CH_2\emptyset + CH_2{=}CH\text{-}\emptyset \qquad (8)$$

$$RCH_2\text{-}\underset{\cdot}{C}H\emptyset + \emptyset \rightarrow RCH_2\underset{\emptyset}{C}H\text{-}$$

$$\xrightarrow{\emptyset CH{=}CH_2} RCH_2CH\emptyset_2 + CH_3\text{-}\underset{\cdot}{C}H\emptyset \qquad (9)$$



(10)



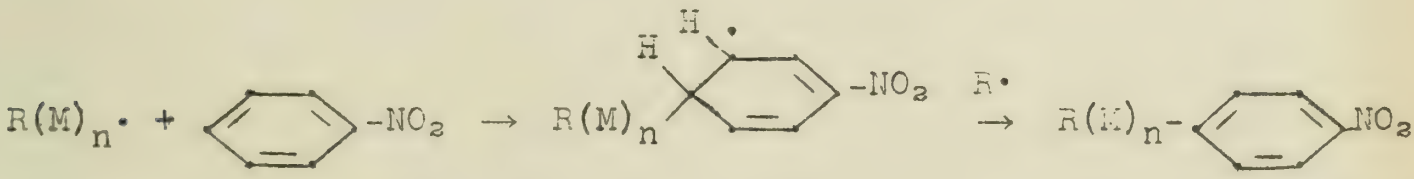
(11)

D. Termination.--Termination appears to be a bimolecular coupling or disproportionation (6,13) although some workers are skeptical (2).

$$2\ R(M)_n^{\bullet} \rightarrow R(M)_n(M)_nR \qquad (12a)$$

$$R(M)_n^{\bullet} + R(M)_n\text{-}CH_2\text{-}\dot{C}HX \rightarrow R(M)_nH + R(M)_nCH{=}CHX \qquad (12b)$$

Retardation of polymerization by inhibitors involves similar termination mechanism (14,15).



+ RH

(13)

The retarding action is due to resonance activation of aromatic nucleus by the nitro group so that the odd electron no longer adds to monomer molecules. The inhibitors were found to be present also as one molecule per polymer molecule.

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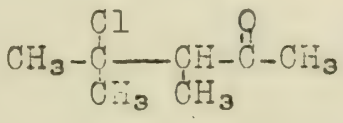
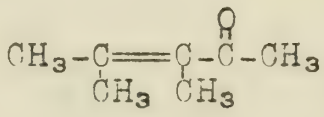
Reported by J. Hwa
December 12, 1947

REACTIONS OF UNSATURATED ACYL CHLORIDES WITH OLEFINS

The reaction of acyl chlorides with olefins has received the attention of chemists since 1892, when the interaction of trimethylethylene and acetyl chloride in the presence of zinc chloride was found to yield the following products:



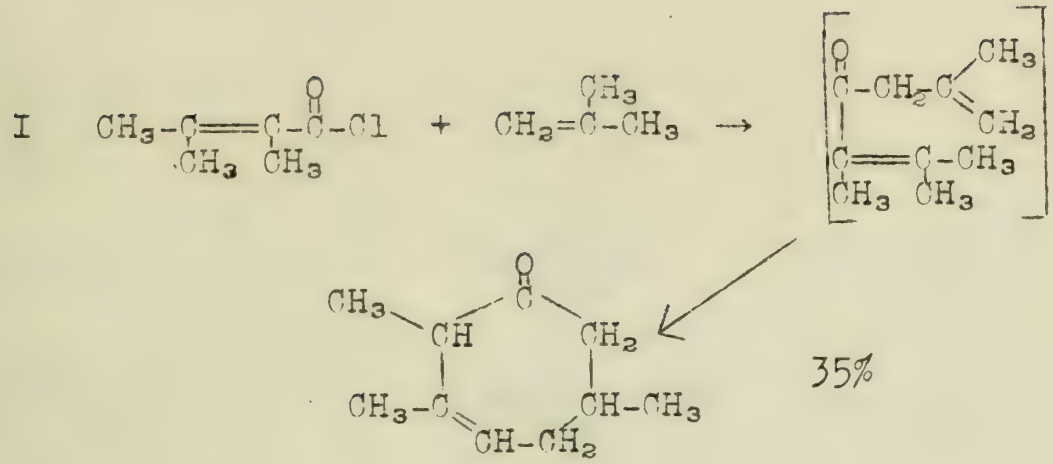


Aluminum chloride as catalyst found application soon thereafter, when the reaction of 2,3,3-trimethylcyclopentene with acetyl chloride was shown to give 1-acetyl-2,3,3-trimethylcyclopentene, the end-product of addition and subsequent dehydrohalogenation. Krapivin (3) studied the action of acetyl chloride and bromide on a series of straight-chain and cyclic olefins in presence of molar or higher amounts of aluminum chloride and bromide, while Darzens (4) found that reaction could be induced by other metal-halide catalysts acting in a similar manner, among them $TiCl_4$ and $SnCl_4$. Darzens and Rost (5) extended the reaction to various higher homologues of acetyl chloride. Colonge and Mostafavi (6) found that the reaction could be more universally applied and yields improved by using catalytic amounts of stannic chloride (10 g. per mole of acyl chloride). Christ and Fuson (7) were the first to try the reaction of an unsaturated acyl chloride with an olefin, and the expected product was obtained: cinnamyl chloride reacted smoothly with cyclohexene in presence of one mole $AlCl_3$ to give cinnamyl cyclohexene-1. A more thorough review of the earlier work on the subject is given elsewhere (8).

Recently Colonge and Dumont (9) presented a systematic study of the reactions of olefins with unsaturated aliphatic acyl chlorides, catalyzed by small amounts of $SnCl_4$. Their procedure consisted in adding slowly five to ten grams of $SnCl_4$ to a mixture of 0.5 mole of acyl chloride and 0.75 mole of olefin; after initial reaction had subsided refluxing was continued for one-half to one hour, the tin complex decomposed with 15% HCl, and the organic layer fractionated; the ketones were obtained from the various fractions as their semicarbazones. The acyl chlorides studied were found to fall under four classifications, depending upon the point of unsaturation in the chain, as well as upon substitution in the α-position:

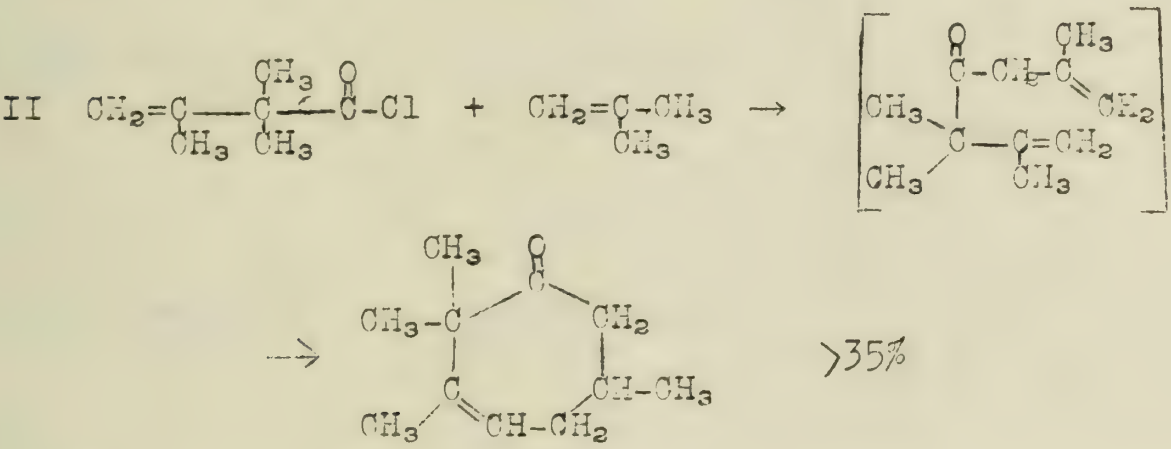
1. <u>α,β-Unsaturated acyl chlorides, unsubstituted in the α-position</u>.--These gave di-unsaturated ketones, formed by acylation of the olefin.

2. <u>α,β-Unsaturated acyl chlorides having an alkyl substituent in the α-position</u>.--Substituted cycloheptenones were obtained as final products:



35%

3. β,γ-Unsaturated acyl chlorides.--Their reaction led to a substituted cycloheptenone via a di-β,γ-unsaturated ketone, which was also isolated in one case:

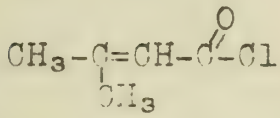
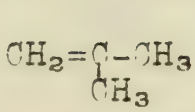
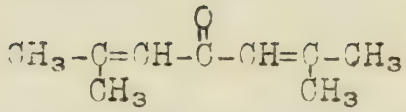
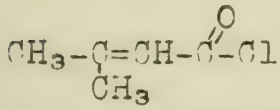
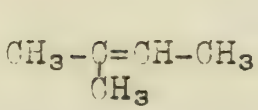
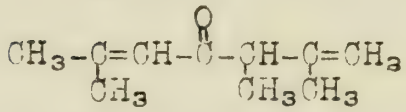
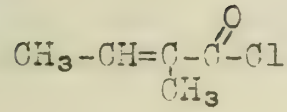
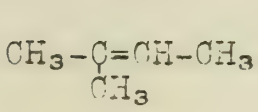
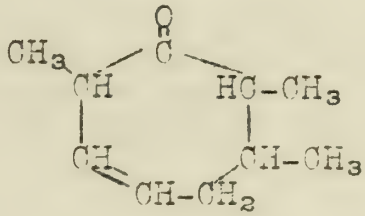
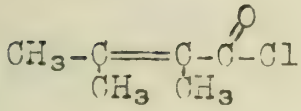
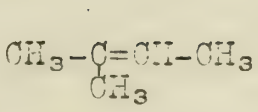
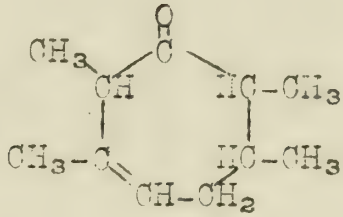
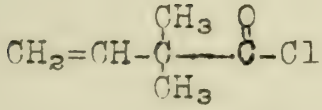
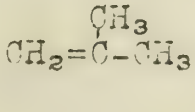
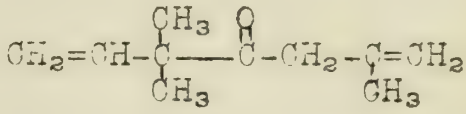
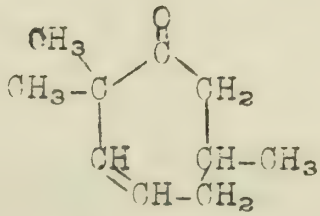
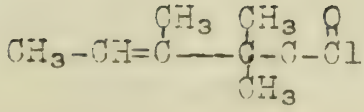
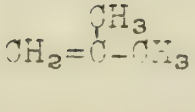
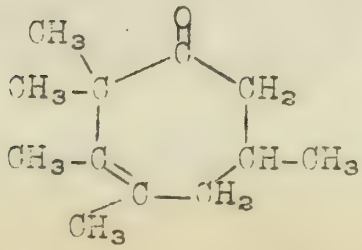


>35%

4. γ,δ- and ω-unsaturated acyl chlorides.--Only straight-chain di-unsaturated ketones were obtained from these.

Some reactions of the above four classes, in addition to those of equations I and II, are listed on page 3. It had previously been found (6) that the β-chloroketone intermediates formed by addition of saturated acyl chlorides to olefins will dehydrohalogenate in either direction to yield mixtures of the α,β- and β,γ-unsaturated products. This explains the β,γ-unsaturation on the olefin side of some of the straight-chain reaction products shown (nos. 2,5,7,8 of table, also eq. II). Unsaturation on the other side of the carbonyl group seems to enhance the unexpected tendency toward β,γ-dehydrohalogenation.

Proofs of Structure of Reaction Products.--Two of the straight-chain ketones were known compounds (nos. 1 - phorone - and 5 , see table). Structures of the others were readily shown by means of ozonolysis. Thus in the product of 2 (table) at least 40% of the total unsaturation was shown to be due to a terminal methylene group.

Acyl Chloride	Olefin	Product	
Class 1			
1) 			48%
2) 		 + "small quantity" of cyclic product, not isolated	>20%
Class 2			
3) 			37%
4) 			43%
Class 3			
5) 		 about	30%
		+ 	<10%
6) 			

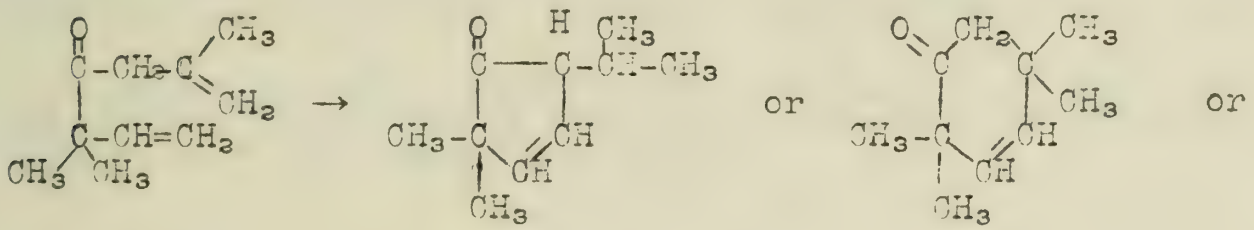
Class 4

7) $CH_2{=}CHCH_2CH_2\overset{O}{\overset{\|}{C}}{-}Cl$ $\quad$ $CH_3{-}\underset{CH_3}{C}{=}CH{-}CH_3$ $\quad$ $CH_2{=}CH{-}CH_2CH_2\overset{O}{\overset{\|}{C}}{-}\underset{CH_3}{C}H{-}\underset{CH_3}{C}{=}CH_2$ 47%

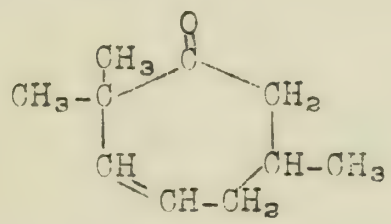
+ $CH_2{=}CHCH_2CH_2\overset{O}{\overset{\|}{C}}{-}\underset{CH_3}{C}{=}\underset{CH_3}{C}{-}CH_3$ 47%

8) $CH_2{=}CH(CH_2)_8\overset{O}{\overset{\|}{C}}{-}Cl$ $\quad$ $CH_3{-}\underset{CH_3}{C}{=}CH{-}CH_3$ $\quad$ $CH_2{=}CH(CH_2)_8{-}\overset{O}{\overset{\|}{C}}{-}\underset{CH_3}{C}H{-}\underset{CH_3}{C}{=}CH_2$ 53%

Of the cyclic products obtained, the structure of only one was proven fully (no. 5 of table). The straight-chain intermediate having been isolated and found to be a known compound, the authors postulated three possible products of its cyclization:



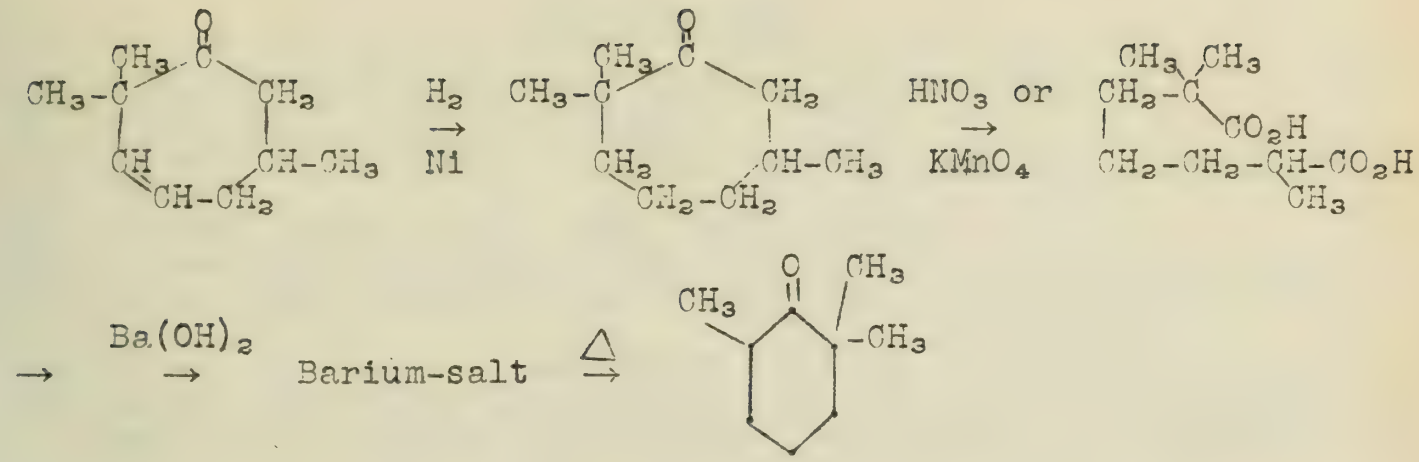
A $\quad$ B



C

The saturated cyclopentanone corresponding to A was prepared by an unambiguous method, and was found to be different from the hydrogenation product obtained from 5. Properties of the latter also did not correspond to those of the saturated cyclohexanone derived from B, which was known. Thus structure C remained as the sole possibility.

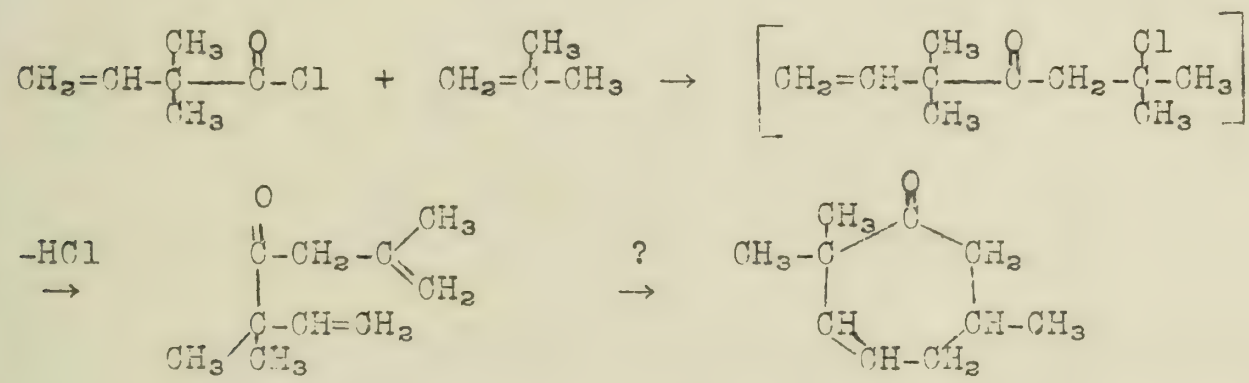
Confirmation of the existence of the seven-membered ring was obtained by the following reactions:



The final product, 2,2,6-trimethylcyclohexanone, was known, and identity was established by melting-points and mixed melting-points with an authentic sample.

Some ambiguity remains regarding the exact location of the double-bond in the ring. In the case of some of the described cycloheptenones calculated and found molar refractivities agree sufficiently to warrant writing the double-bond out of conjugation with the carbonyl-group. In other cases such data are inconclusive.

Mechanism.--The course of the reaction is certain only up to the point of formation of the straight-chain di-unsaturated ketone. Taking no. 5 (see table) as example:



The authors fail to state a satisfactory mechanism for the cyclization. Actually it is rather hard to find a reasonable explanation based on acceptable premises. That cyclization takes place via the intermediate shown, and not directly from the β-chloro-ketone, was demonstrated in the above case by formation of the identical cycloheptenone from the isolated straight-chain ketone by heating in a mixture of sulfuric and acetic acids.

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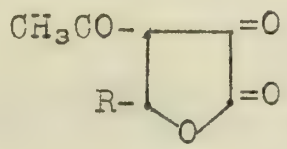
Reported by Frank X. Werber
December 12, 1947

PREPARATION AND PROPERTIES OF α-KETO-γ-LACTONES

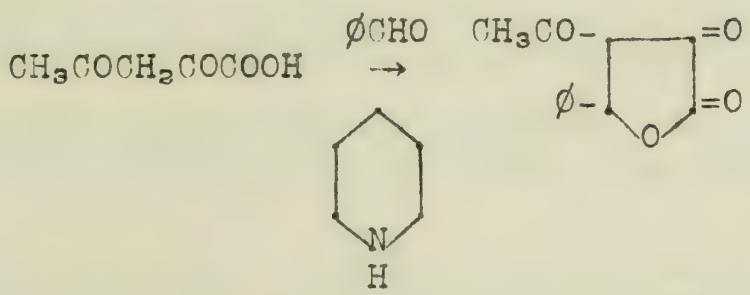
I. Introduction.--In the course of investigations upon natural products during 1941-44, Schinz and Hinder (1) devised a scheme for preparing various α-keto-γ-lactones with substituents in the β as well as the γ position.

II. Historical.--Claisen (2) reported the first α-keto-γ-lactone in 1891.



A number of other workers have prepared similar compounds in which the β substituents are acyl (3,4), carbethoxy (5), phenyl (6), and the γ substituent a phenyl group in each case. Ruhemann (3) ascribed the name "paracone" to compounds of this type.

The general procedure was to condense benzaldehyde with a compound containing an active methyl or methylene group in the presence of a basic catalyst such as piperidine:

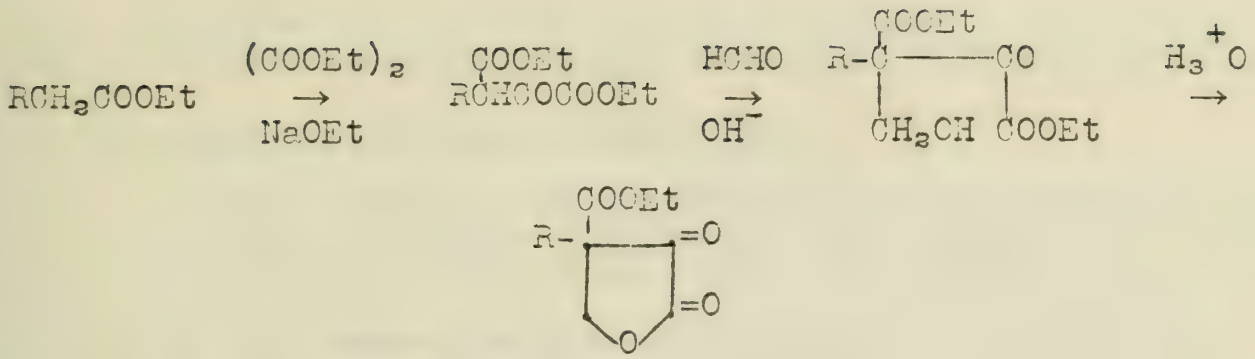


Erlenmeyer (6) attempted to prepare α-keto-γ-alkyl-γ-lactones but was unsuccessful.

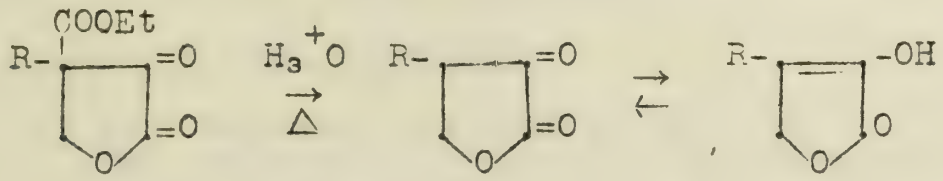
The β,β-dimethyl homologue was reported by Kuhn and Wieland (7) in 1942, but prior to the work of Schinz and Hinder, it appears that the β-monoalkyl derivative had not been prepared, although the unsubstituted α-keto-γ-lactone has been known since 1915 (8).

III. Preparation of α-Keto-γ-Lactones.--The synthesis of these compounds proceeds in a manner analagous to that outlined by Claisen (2) for the β-acyl-γ-alkyl derivative.

A. α-Keto-β-Alkyl-β-Carbethoxy-γ-Lactones.--By the method of Arnold (9) and Mebus (10) the α-ethoxalyl derivative of a fatty ester is made and treated with aqueous formaldehyde in the presence of an alkaline catalyst such as potassium carbonate or pyridine. Ring closure is effected by acidification of the reaction mixture.



B. α-Keto-β-Alkyl-γ-Lactones.--These are obtained by heating the β-carbethoxy derivative in dilute sulfuric acid.

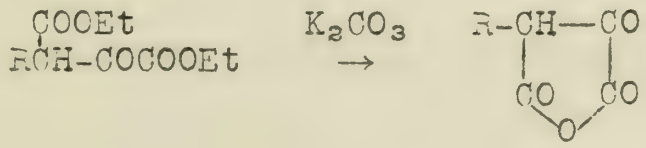


C. α-Keto-β-Acyl-γ-Lactones.--Prepared by substituting a methyl ketone for the fatty ester.

D. γ-Substituted Lactones.--Obtained by substituting the appropriate aldehyde in the aldol type condensation.

E. Anomalous Reactions.--Attempts to prepare α-keto-γ-alkyl-γ-lactones and α-keto-β-aryl-γ-lactones by a similar method resulted in α,β-unsaturated esters.

An attempt to prepare α-keto-β-carbethoxy-β-(n-amyl)-γ-methyl-γ-lactone by condensing α-ethoxalylheptylic ester with acetaldehyde in the presence of potassium carbonate failed. Instead a substituted α-ketosuccinic anhydride resulted. The reaction is general.



IV. Properties of α-Keto-γ-Lactones.--

A. α-Keto-β-Carbethoxy-γ-Lactones (1,11,12).--

1. The β-unsubstituted compound is solid. All others prepared were liquid at room temperature.
2. With alcoholic $FeCl_3$ the β-unsubstituted member gave a deep red color. The others gave none.
3. In aqueous solution all reacted acid to congo red.

4. The lactone ring is easily opened.
5. The lactones undergo decarboxylation very readily.

B. <u>α-Keto-β-Monoalkyl-γ-Lactones</u>.--

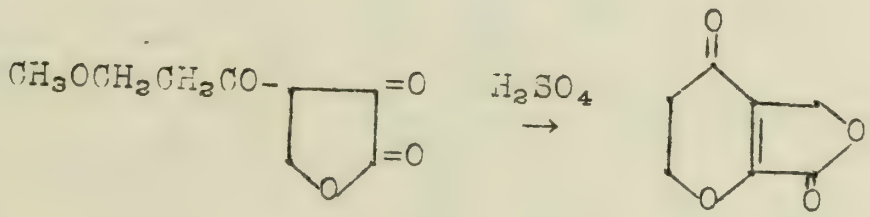
1. The β-methyl and β-unsubstituted homologues are solids. The others are liquids at room temperature.
2. All compounds in this group are completely enolized (13,14).
3. All compounds give a deep red color with $FeCl_3$.
4. The enols can be titrated with 0.1 N NaOH.
5. The lactone ring is stable to alkali.
6. The lactones quickly decompose in the air to form oxalic acid and a ketol.
7. Thermal decomposition occurs at about 300°, resulting in α-substituted acroleins.

C. <u>α-Keto-β-Acyl-γ-Lactones</u>.--

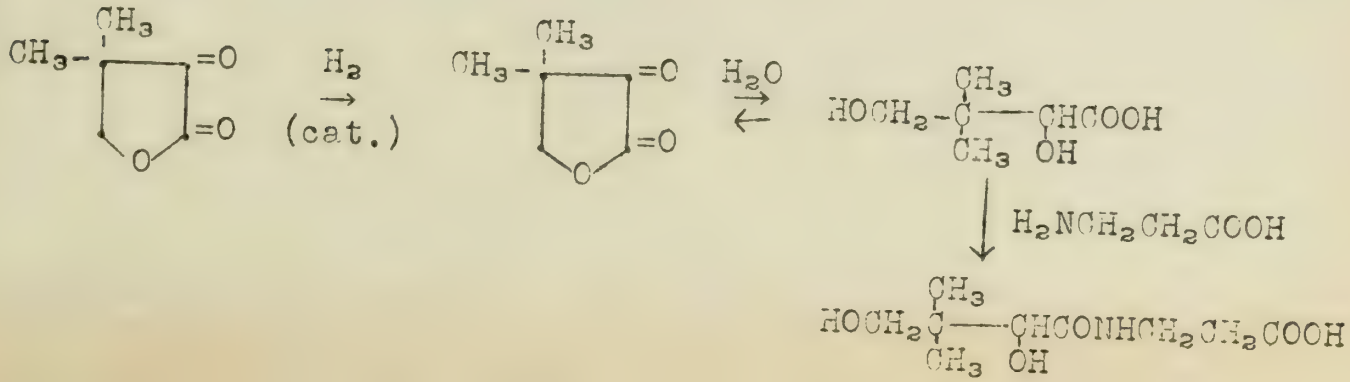
1. All compounds prepared are solids.
2. The lactones exist chiefly in enolic form.
3. Compounds are easily brominated.
4. Compounds are acid to litmus.

V. <u>Uses of α-Keto-γ-Lactones</u>.--As already implied, one of the uses of these compounds is as a stepping stone in the synthesis of natural products.

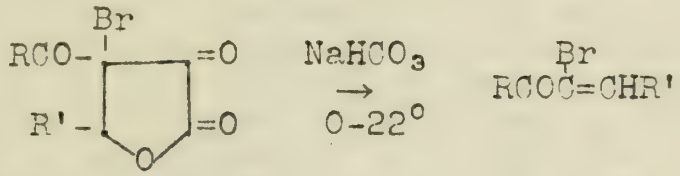
A. Thus Peutzer, Nield, and Barry (15) synthesized a clavacin isomer, going through an α-keto-γ-lactone:



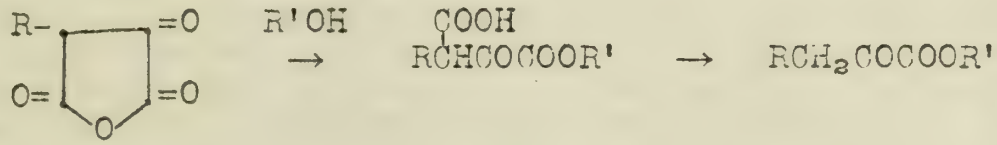
B. Kuhn and Wieland (7) devised a synthesis for pantothenic acid.



C. Nield (12) turned the reactivity of the β-bromo-β-acyl-lactones to good use in the preparation of α-bromo-α,β-unsaturated ketones and esters.



D. Although Schinz and Hinder (1) failed to make the β,γ-disubstituted-γ-lactone, they hit upon a good use for the substituted α-ketosuccinic anhydride they obtained. By treating the anhydride with an alcohol and subsequent decarboxylation, one can obtain an α-keto ester one carbon longer than the original acid.



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Reported by R. H. Mattson
December 12, 1947

VAPOR PHASE NITRATION

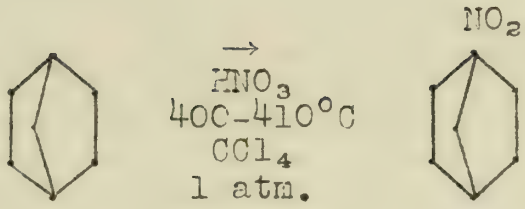
The familiar nitration is a liquid phase reaction. The compound to be nitrated must accordingly be below its critical temperature or be dispersed in some solvent in order to carry out the reaction. The saturated alkanes of less than five carbon atoms are above their critical temperatures at normal nitration temperatures. At the same time they are quite unreactive toward nitrating reagents due, to a large extent, to their extreme insolubility. Meyer, in 1872, had obtained nitroalkanes by the interaction of an alkyl halide and silver nitrate (1). Beilstein and his associates had secured nitrocyclohexane by a liquid phase nitration of a petroleum fraction (2). In 1936, Hass, Hodge, and Vanderbilt of Purdue University reported the successful nitration of propane, butane, and isobutane. Since then Hass and his coworkers have reported the nitration of methane, ethane, isopentane, pentane, 2,2-dimethylpropane, 2,3-dimethylbutane, 2,2-dimethylbutane, 2,2,3-trimethylbutane, cyclohexane, cyclopentane, cyclopropane, and bicyclo(2,2,1)heptane (3). To carry out these reactions they have developed a process for vapor phase nitrations. In this process the hydrocarbon and nitrating reagents are first preheated separately, then injected simultaneously into a tube reactor through which they pass in a fraction of a second at an elevated temperature. The product is trapped by cooling to separate it from the gaseous by-products. The vapor phase reaction allows intimate contact between reagents and escapes the usual difficulty of mixing a gaseous hydrocarbon with a liquid nitrating agent.

In the Industrual and Engineering Chemistry for July 1947, Hass and Schecter list thirteen rules which appear to govern the vapor phase reaction. In the interests of completeness these will be listed below. Insofar as possible, however, emphasis will be placed upon those findings which have not been set forth in standard lectured courses in organic chemistry.

Rule 1.--At nitration temperatures between 150°C and 475°C no carbon skeletal rearrangements occur. Since nitroneopentane is obtained from neopentane and neohexane, the reaction does not appear to involve a carbonium ion (4). While the temperatures are not high enough to cause isomerization, they are sufficient to cause the decomposition of the lower nitro compounds. Nitroethane and 1-nitropropane have been observed to yield olefins, aldehydes, and other decomposition products but no lower nitroalkanes (5).

Rule 2.--Nitration of saturated hydrocarbons at temperatures ranging from 228° to 710°C has not been observed to produce polynitroalkanes. The identification of such compounds by other workers (6,7,8) is in question. As higher homologues are prepared, this rule may require alteration.

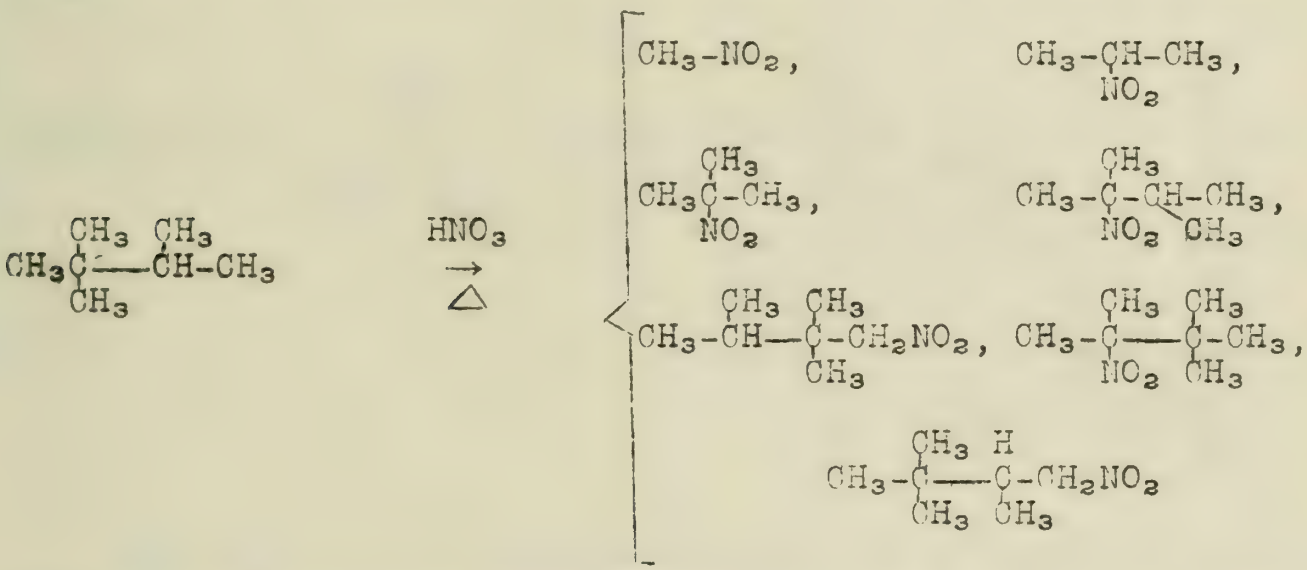
Rule 3.--Any primary, secondary, or tertiary hydrogen atom in a hydrocarbon is capable of being substituted by a nitro group. Although Nametkin (9) was unable to effect the tertiary nitration of camphane in the liquid phase reaction, the tertiary nitro compound from bicyclo-(2,2,1)-heptane is obtained in good yield from the vapor phase nitration (10).



50% of product

The remainder of the product is a mixture of secondary nitro derivatives. This is further substantiation for a frontal attack mechanism.

Rule 4.--The nitro group can replace any alkyl groups in an alkane but no fission occurs in unsubstituted monocycloalkanes.



Rule 5.--Highly branched hydrocarbons undergo less fission during nitration than do their less branched isomers.

Hydrocarbon	Ratio: $\frac{\text{fission products}}{\text{substitution products}}$
n-Pentane	0.745
2-Methylbutane	0.628
2,2-Dimethylpropane	0.370

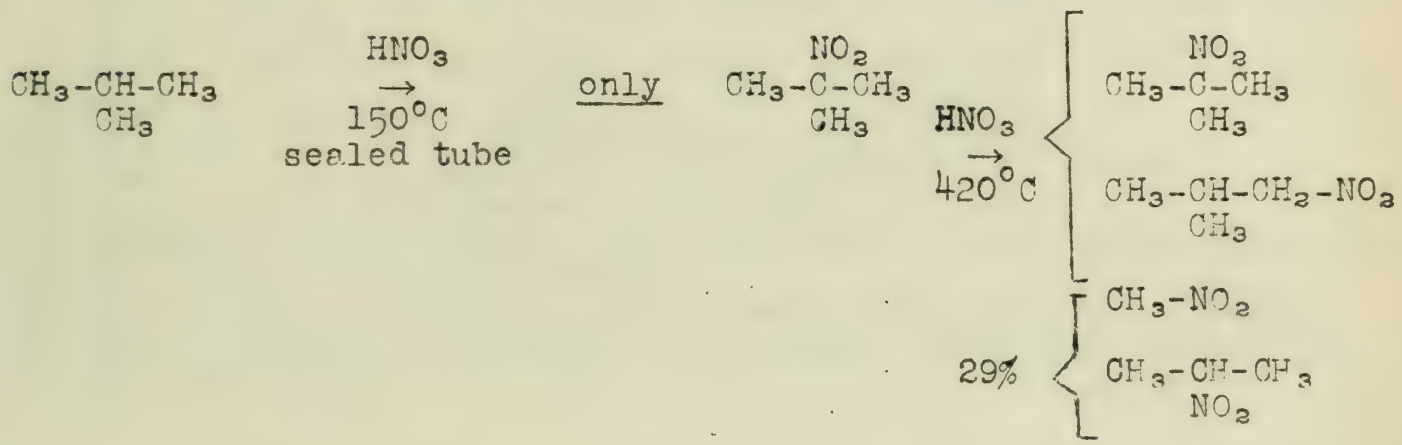
Since nitration-producing fission is primarily a competing and not a consecutive reaction, it is believed that these results are due to a steric effect.

Rule 6.--Although nitrogen dioxide and nitric acid yield identical products, duplicate experiments showed about four times as great a yield with nitric acid as with nitrogen dioxide.

Rule 7.--Oxidation accompanies nitration-yielding acids, aldehydes, ketones, alcohols, nitrites, nitroso compounds, nitro-olefins, polymers, carbon monoxide, and carbon dioxide. Formaldehyde hydroxylamine, and hydrogen cyanide together with ammonium nitrate have been formed during the nitration of methane. Little nitric acid is reduced to nitrogen. In fact, if the nitric oxide removed from the reaction is converted back to nitric acid, a yield of 90 per cent of theoretical based upon the consumption of nitric acid to form nitro compounds is obtained.

Rule 8.--Reaction rates are greatly accelerated at increased temperatures. Methane is quite difficult to nitrate, ethane somewhat easier, and compounds above propane appear to be of about the same order of reactivity.

Rule 9.--As the reaction temperature is increased, the quantity of fission products increases with respect to substitution products. Thus:



Rule 10.--At low temperatures the rate of substitution is in the order tertiary > secondary > primary. As the temperature is increased, the ease of substitution approaches equality. Contributing factors are probably: (a) convergence in the primary, secondary, and tertiary positions, (b) high ratio of primary hydrogen atoms, (c) greater stability of the primary nitroalkanes at higher temperatures, and (d) relative stereochemical ease for primary substitution.

Rule 11.--Below the optimum nitration temperature for a particular compound, the conversion falls off rapidly due to incomplete reaction. Above the optimum temperature the yield falls off rapidly due to oxidation. In practice, it has been found necessary to regulate the temperature of nitration to within 1°F.

Rule 12.--Elevated pressures increase the reaction rate but have little effect of yield (11). The yield of nitro paraffins increases with the hydrocarbon concentration up to a mole ratio of about 15:1. Explosive tendencies result with high nitric acid to hydrocarbon ratios.

Rule 13.--Silica gel, nitric oxide, platinum oxide, iron,

copper, lead, and the heavy metal oxides catalyze oxidation side reactions and thus decrease the yields of nitroparaffins. Light, aluminum nitrate, or carbon monoxide have no appreciable effect on the reaction. Suitable construction materials are glass, silica, platinum, and gold. Chromium-nickel steels are satisfactory if a mixture of sodium and potassium nitrate is continuously sprayed into the reactor.

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Reported by O. C. Keplinger
December 12, 1947

PARTITION CHROMATOGRAPHY

Any process designed to separate materials having similar properties must be fractional in nature, that is, the overall separation is the result of a number of operations in each of which the mixture is enriched slightly in one of the components. If each of these operations must be carried out separately the process is very time-consuming, but when they can be combined into one step, as is the case with the chromatographic technique, a convenient and powerful tool for effecting difficult separations results. In 1941, Martin and Synge (1) conceived the idea of replacing the adsorbent in a chromatographic column with a non-mobile liquid phase so that the resulting process would be a fractional extraction rather than a fractional adsorption. They coined the name "partition chromatography" for this new technique.

General Procedure.--The problem of obtaining an immobile liquid phase is solved by adsorbing the desired liquid on an inert, finely divided solid which has no affinity for the materials to be passed through the column. Most workers have used water as the stationary liquid; adsorbents which have been used include silica gel, potato starch and filter paper. Recently the use of nitromethane adsorbed on silica gel has been reported (2). After the column has been packed evenly with the desired liquid-solid combination, the mixture to be separated is dissolved in a non-polar solvent and passed into the top of the column. The components of the mixture all migrate at once to the polar, stationary liquid phase. The chromatogram is then developed by the usual technique using more and more polar liquids to wash the dissolved materials down the column. The rate at which each component moves down the column is a function of the partition coefficient of that component between the immobile liquid and the washing solution.

Methods for following the progress of the bands are essentially the same as those used in adsorption analysis. Colored materials act as their own indicators, acidic and basic substances may be followed by suitable indicators dissolved in the stationary liquid phase, and fluorescent materials may be observed under ultra-violet light. If it is not possible to follow the progress of the bands in the column, the washing may be carried on for a definite period of time and then the column may be extruded and streaked with reagents which give color tests with the dissolved materials. An alternative is to collect the eluate in small fractions at the bottom of the column and analyze these fractions for the presence of the desired materials. Substances which do not wash out of the column may be removed by slurrying the extruded column with solvents such as acetone.

An interesting variation of the chromatographic technique was used by Consden, Gordon and Martin (3), who replaced the customary column with a sheet of filter paper containing adsorbed water. However, since provision had to be made to maintain constant and high humidity around the paper, the apparatus as a whole was more complicated than the column it replaced.

Applications.--1. Separation of acetylated amino acids (1,4,5,6) - The first practical application of partition chromatography was to this problem. Water on silica gel was used in the column, and chloroform containing small amounts of butanol proved to be the best wash liquid. Satisfactory analyses of wool and gelatin hydrolyzates for amino acids have been obtained with this system.

2. Separation of free amino acids (2,7,8) - Free amino acids cannot be separated on a silica gel - water column, but if potato starch is substituted for the silica gel and the acids are washed down the column with butanol, good separations can be obtained. Protein hydrolyzates have been analyzed successfully in this manner.

3. Separation of methylated glucoses (9) - Di-, tri-, and tetramethylglucoses resulting from methylation and degradation of glucopolysaccharides have been separated quantitatively on silica-water columns washed with chloroform and chloroform-butanol. This separation has always been the most difficult step in structure studies of starches and cellulose.

4. Analysis of commercial hexachlorocyclohexane (2) - Although the separation of alpha, beta, gamma, and delta isomers of this material can be accomplished only with considerable effort by crystallization techniques, it has been possible to obtain almost quantitative separation of a commercial product into these components by partition chromatography on a column of nitromethane-silica gel, using hexane as the wash liquid. The method also served to isolate some hepta- and octachlorocyclohexane.

5. Separation of carbonylic acids (10,11) - The series of acids from formic to valeric has been separated into its components by partitioning chromatographically between silica gel-water and chloroform-butanol. The location of the acids was shown by bromcresol green dissolved in the aqueous phase. It is interesting to note that in this case there was no distinct separation between butyric and isobutyric acids.

6. Separation of amines (12) - It has been shown in this laboratory that partition chromatography can be used to separate amines by partition between silica gel-water and organic solvents. Aniline was separated from mono and dimethylanilines by using ethyl ether as the organic liquid and by buffering the water to a pH of 2-3. It is interesting to note that with acids or bases having different dissociation constants, the effectiveness of separation varies with the acidity of the aqueous phase.

Summary.--1. Advantages of the method - The equipment involved is simple and inexpensive, yet may be used to effect some rather difficult separations. The method involves no high temperatures or strong acids or bases which might damage sensitive compounds. It is also equally applicable to volatile and involatile materials, in contrast to fractional distillation. Since there is

never any strong adsorption involved, almost quantitative recovery of starting materials is possible. It is possible to work with very small amounts of materials and still obtain good results.

2. Disadvantages of the method - A certain amount of technical skill must be acquired to handle this type of work effeciently. The amounts of material which can be fractionated are limited by the size of the column, since it is best to work with fairly dilute solutions. The solvent pairs which can be used are limited somewhat by the fact that one of them must be adsorbed rather tightly on the solid in the column and the other not at all. Compounds which ionize in one solvent and not in the other show considerable changes in partition coefficions with changes in total concentration and are sometimes difficult to work with.

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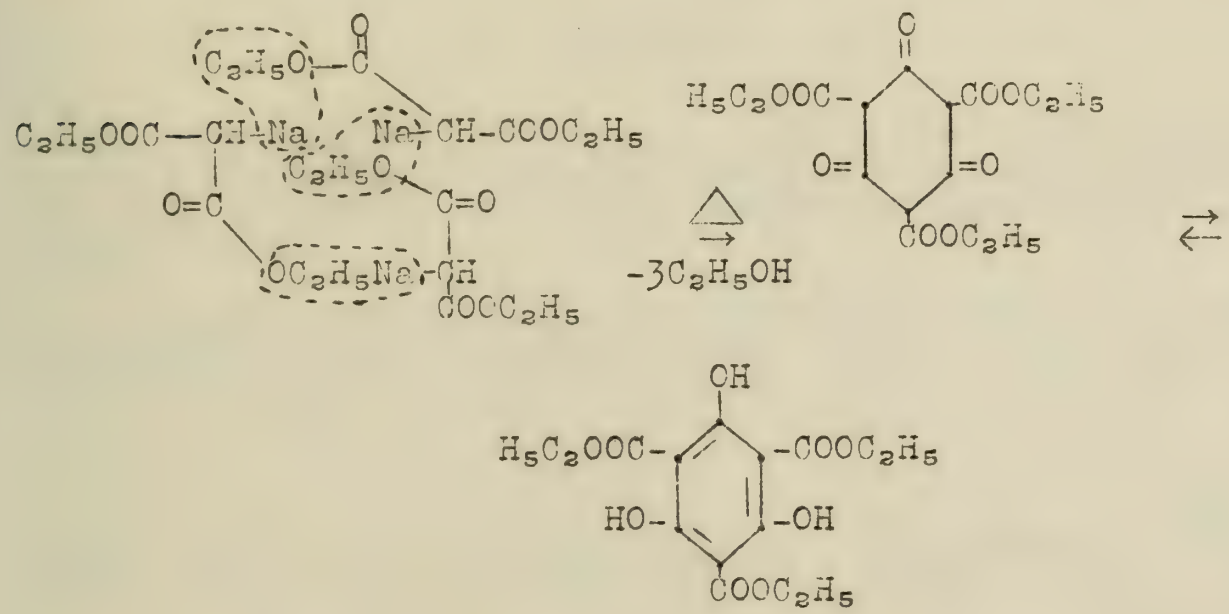
Reported by John C. Richards
December 19, 1947

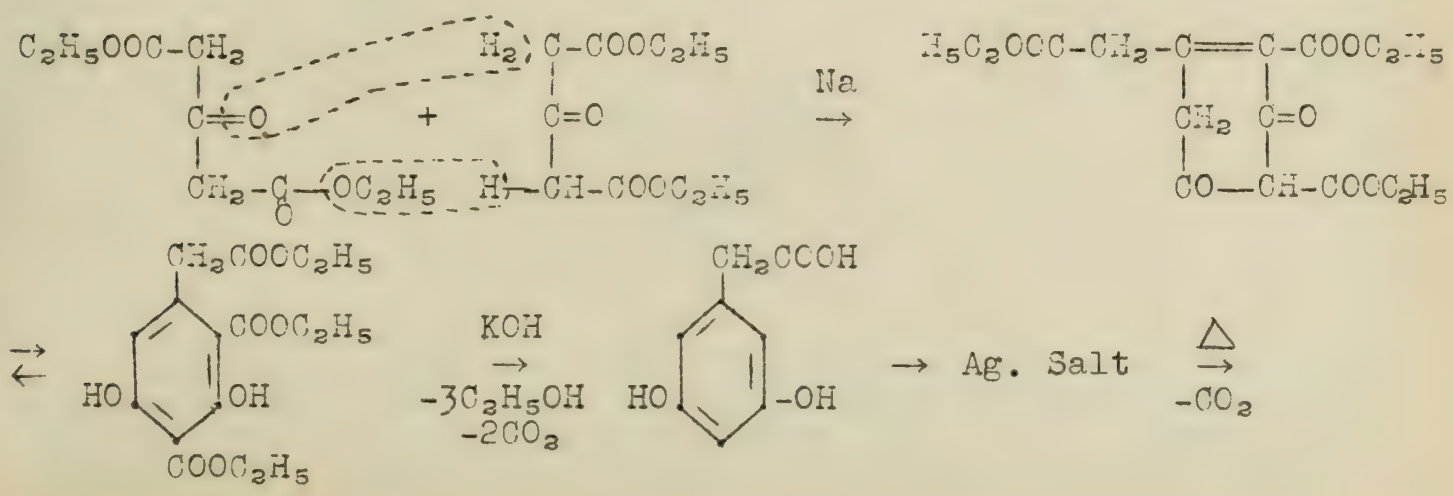
FORMATION OF SUBSTITUTED PHENOLS BY CONDENSATION OF ALIPHATIC COMPOUNDS

Baeyer in 1885 found that sodio malonic ester when heated to 120-145° with excess malonic ester yields triethyl trihydroxy trimesate (1). This reaction is formally similar to the acid cata-

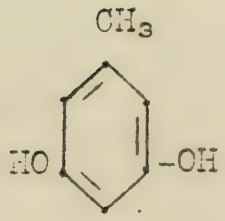


lyzed self-condensation of acetone to form mesitylene. Potassium hydroxide fusion of the product brings about saponification and decarboxylation to phloroglucinol.

It was soon realized that this type of reaction was not only of preparative interest, but might also throw light on the synthesis of phenols by plants. The self-condensation of diethyl acetonedicarboxylate - a substance of close structural relationship to citric acid - was studied and shown to yield the ethyl ester of a tribasic phenolic acid, decarboxylation of which gave orcinol, the parent substance of many aromatic compounds found in the plant kingdom (2). The structure of the intermediate triester was proved



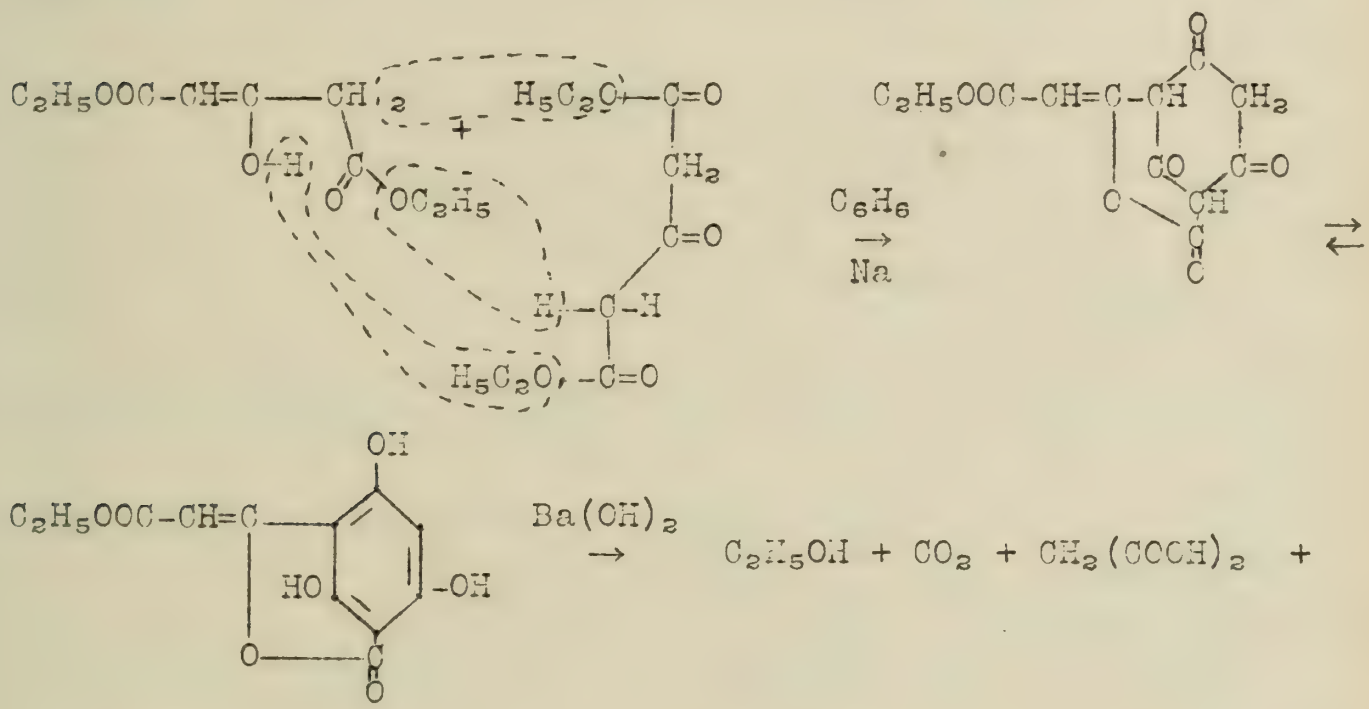
yield up to 50%



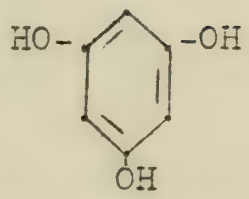
orcinol

a few years later (3). It was also shown that the condensation may be brought about by heating diethyl acetonedicarboxylate with alcoholic HCl (4) or by heating dimethyl acetonedicarboxylate by itself (5).

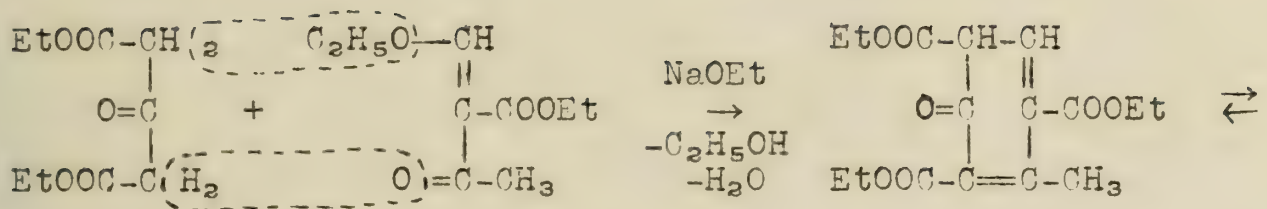
A slight alteration of the conditions in the self-condensation of diethyl acetonedicarboxylate will lead to a phloroglucinol derivative (6).

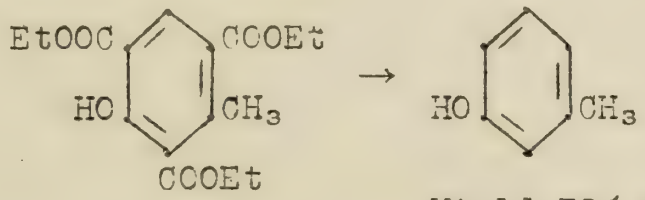


60-70% yield

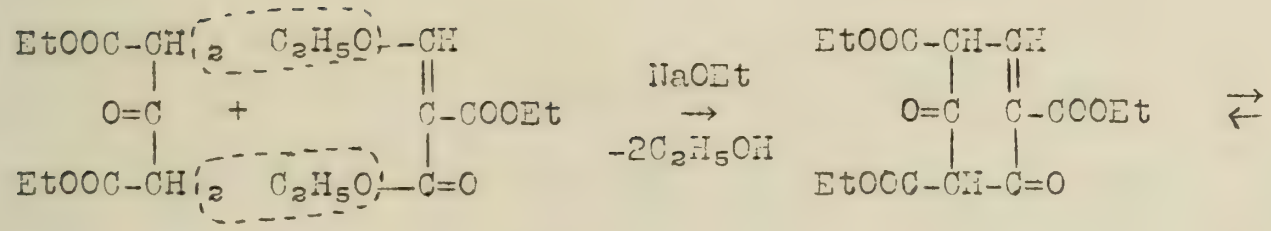


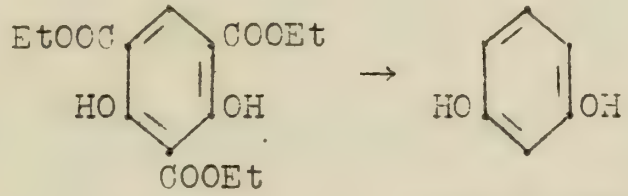
The condensation of diethyl acetonedicarboxylate with ethoxymethylene acetoacetic ester (7) and ethoxymethylene malonic ester (8) followed by decarboxylation yields m-cresol and resorcinol respectively. These condensations involve the two active methylene groups of diethyl acetonedicarboxylate and the carbonyl and/or ethoxy groups of the other component.





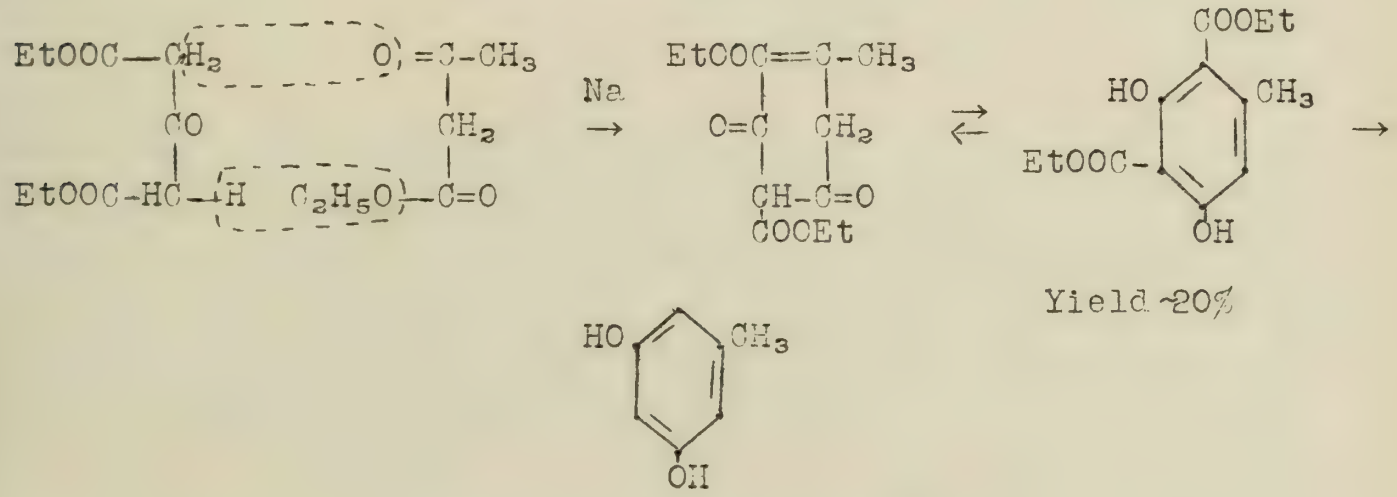
Yield 72% (of ester)





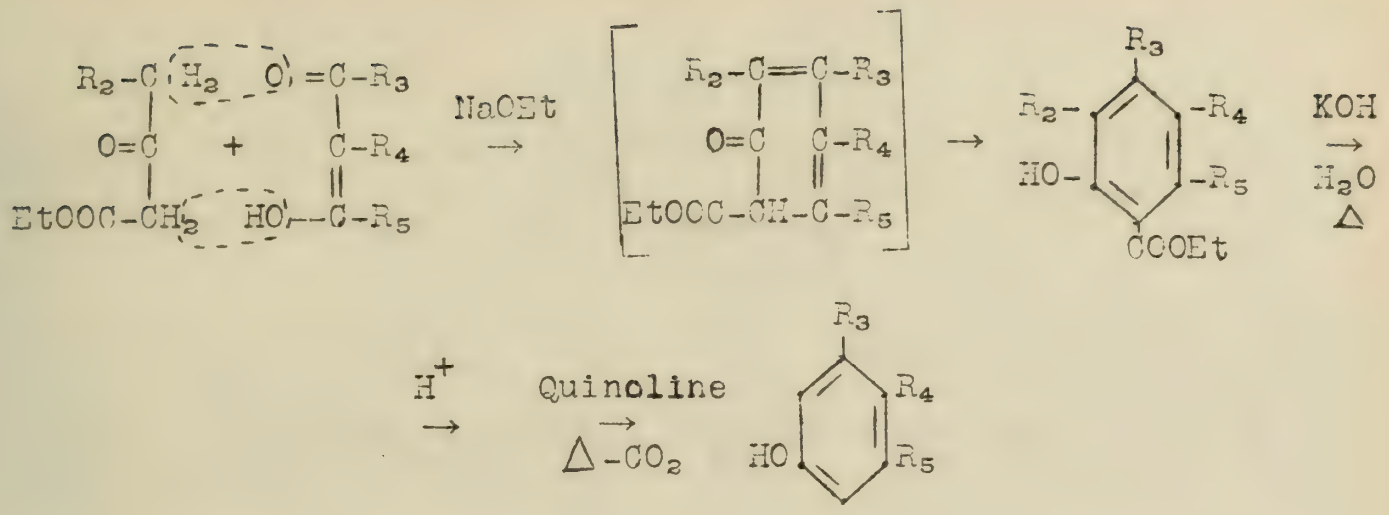
Yield ~30% (of ester)

The condensation of diethyl acetonedicarboxylate with ethyl acetoacetate leads to orcinol (9).



Yield ~20%

Recently a systematic study of the condensation of ethyl acetonedicarboxylate and ethyl acetoacetate with β-diketones and ketoaldehydes has been undertaken (10). The reaction proceeds according to the general scheme:



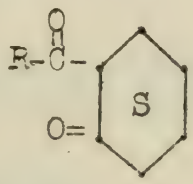
Examples:

WITH DIETHYL ACETONEDICARBOXYLATE (R_2 = EtOOC-)

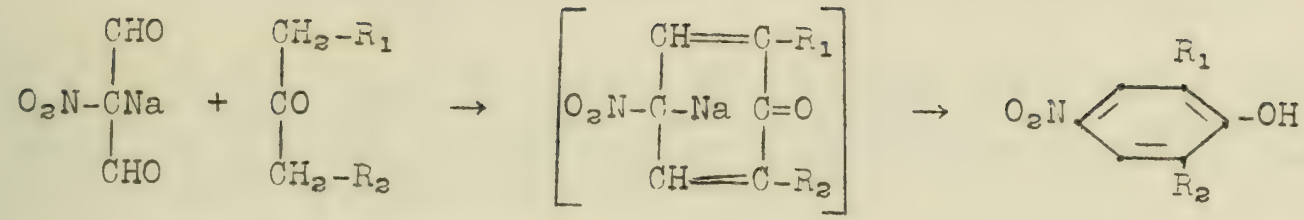
R_3	CH_3	n-$C_{15}H_{31}$	CH_3	C_6H_5	CH_3	$-(CH_2)_3-$	$-(CH_2)_4-$	$-(CH_2)_4-$	$-(CH_2)_4-$
R_4	H	H	H	H	H				
R_5	H	H	CH_3	H	C_6H_5	H	H	CH_3	COOEt
Yield %	49	~65	92	59	47	96	83	36	79

(All yields refer to the intermediate ester. Decarboxylation yields are of the order of 90%.)

With ethyl acetoacetate (R_2=H) the yields were substantially lower (18-55%) in the three cases studied.

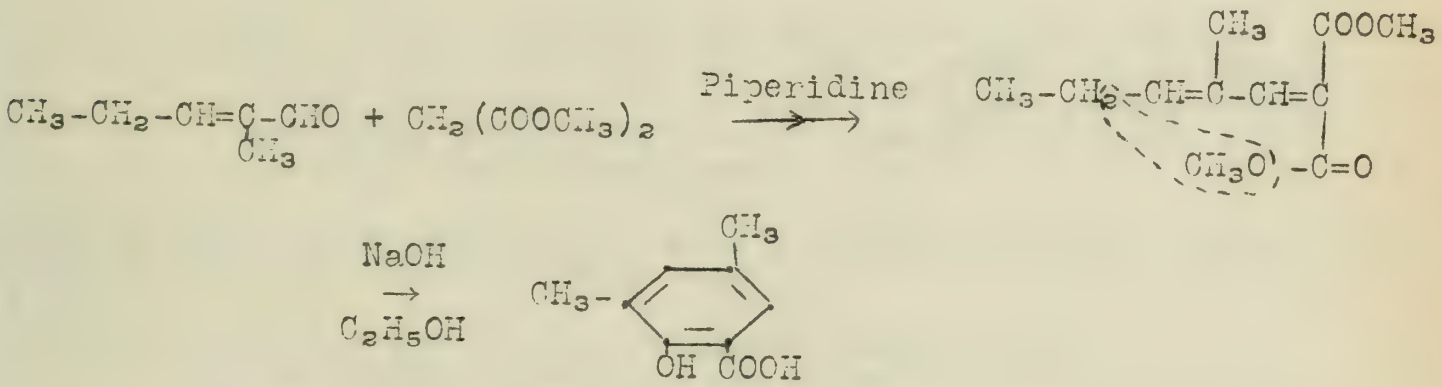
If cyclic diketones of the type  are used (last four examples in the table) the products might be useful as an intermediate in the synthesis of estrogenic hormones. A few similar condensation reactions that have been reported are the self-condensation of acetyl pyruvic ester to yield 3-methyl-5-hydroxy benzoic acid and m-cresol (11); the condensation of ethoxymethylene acetoacetic ester with acetoacetic ester to yield 4-hydroxy-6-methyl-isophthalic acid and m-cresol (12) and the condensation of methoxymethylene cyclohexanone with acetoacetic ester to yield ar-3-carboxy-2-tetralol (13).

The reaction of the sodium salt of nitromalonic aldehyde with ketones having two free methylene groups has been used in the synthesis of substituted p-nitrophenols (14, 15, 16).



R_1	H	H	C_6H_5	C_6H_5	H	H	COOEt	COOEt	o-tolyl	m-tolyl
R_2	H	CH_3	C_6H_5	C_6H_5	COOEt	CH_2COOEt	COOEt	COOEt	o-tolyl	m-tolyl
Yield %	?	88	94.5	81	90	82	90	84.6	74.4	86.5
Ref.	14	15	15	16	15	15	15	16	16	16

A somewhat different type of condensation leads to substituted salicylic acids from which phenols might be obtained by decarboxylation (17).



Citral reacts similarly to α-methyl-β-ethyl acrolein; but the reaction does not seem to be very general and the yields are poor.

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Reported by Ernest L. Eliel
December 19, 1947

A DESIGN FOR THE NOMENCLATURE OF POLYCYCLIC SYSTEMS

A system, based in part on the bridging principle of Grignard, has been proposed by G. Dupont and R. Locquin. The authors seek to establish a system of nomenclature that is uniform for all derivatives of a reference system.

A "fundamental nucleus" or "base nucleus" is chosen to which all other rings of the system are attached by at least one atom (See examples I and II). A "simple nucleus" is defined as a system or part of a system containing valence bridges only. A "dihedral nucleus" is defined as one containing one or more atomic bridges. The base nucleus is called the primary cycle and all other rings of the compound are called secondary cycles. A number of rules of priority are used in selecting the base nucleus. They can be summarized as follows:

I. Rules of priority of structural order.
   a. the cycle containing 6 atoms, afterward 5,7,8,9...4 and finally 3.
   b. the cycle containing the most valential bridges.
   c. the cycle containing the fewest hetero (non-carbon) atoms, afterward hetero atoms of least atomic weight.
   d. the <u>ortho</u> condensed cycles, then <u>peri</u> spiranic, and finally β and γ condensed cycles.

If two cycles present the same structural peculiarities, it is necessary to use the following rules.

II. Rules of priority of chemical order.
   a. the cycle containing the fewer functional groups.
   b. the cycle containing the fewer purely hydrocarbon substituents.
   c. all other choices equal, alicyclic rings have priority over aromatic rings.
   d. the cycle whose functional groups are the farthest from the base nucleus.
   e. the cycle containing hydrocarbon substituents of less weight or less branched.

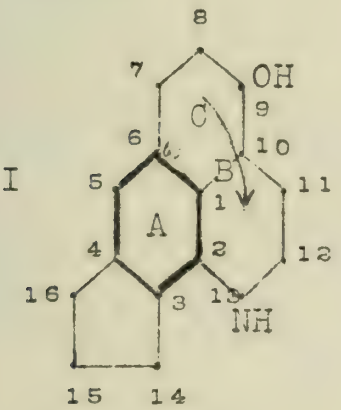
<u>Numbering the compound</u>.--Before the compound can be numbered, it is necessary to select a starting point and direction of numbering. This is done as described below. The largest secondary group is found. It is called the guide group. From the guide group is chosen a guide ring and guide atom, which is the atom of departure for numbering, The guide ring is usually the first ring of the guide group, and the guide atom is the first atom joining the guide ring to the base nucleus. Naturally they depend upon the direction of numbering. Once the guide atom and direction of numbering have been chosen, the numbering proceeds around the base nucleus and on to the other rings, including all ring members. The direction of numbering, guide ring, and guide atom are chosen in such a manner as to proceed from the reference atom toward the heart of the guide group and then toward the other groups, passing only a minimum number of atoms of the base nucleus in going from one bridge to another. The guide ring should be <u>ortho</u> or

peri spiranic condensed to the base nucleus. Numbering begins with the first atom after the guide atom. The direction of numbering in the secondary rings, lying in the same plane as the principal part of the base nucleus, is the same as in the base nucleus. Numbering of bridges outside the plane proceeds from the atom of lower number in the base nucleus toward the atom of higher number.

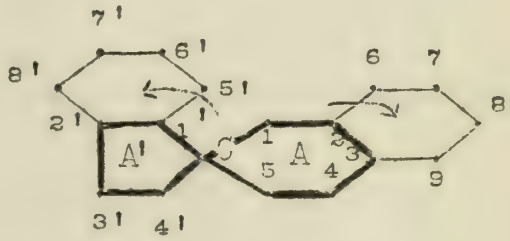
When numbering complex spiro systems, each part of the system connected by the spiran atom is considered as a separate system. Numbering proceeds from the spiran carbon (called the "zero" carbon) in a direction confirming to the rules for other compounds. The numbers of the atoms of the secondary component are primed.

Examples:

I



II

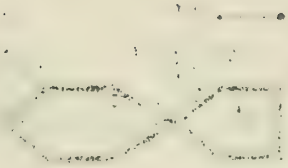


A - base nucleus
B - guide group
C - guide ring
G - guide atom

Formation of the name.--The name of a polycyclic compound comprises:

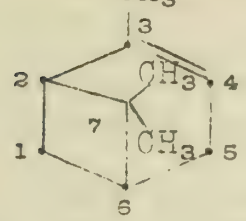
1. a "key", indicating the nature of the component rings, whether aliphatic (Ali) or aromatic (Aro) or both, the number of rings and the formula of the ring members.
2. an indication of the nature and position of substituents not in the base nucleus.
3. an indication of the bridges not in the base nucleus.
4. the name of the base nucleus with its substituents.

"Gephyro" means a saturated bridge, "gephyreno", and "gephyrodieno", etc., unsaturated bridges. The series of numbers characterizing the bridges are arranged in columns or linearly in parentheses. A benzene, pyridine, pyrrole, furan, or thiofene ring is designated by the symbol $\triangle$, placed before the first atom of the double bond. With spiro complexes, each part is named separately. The names are put in parentheses and are joined by the word "spiro". The formula of the ring members is given thus: $C_y{>}C{<}C_x$ where y and x are the number of atoms in the secondary and primary components respectively.



Examples:

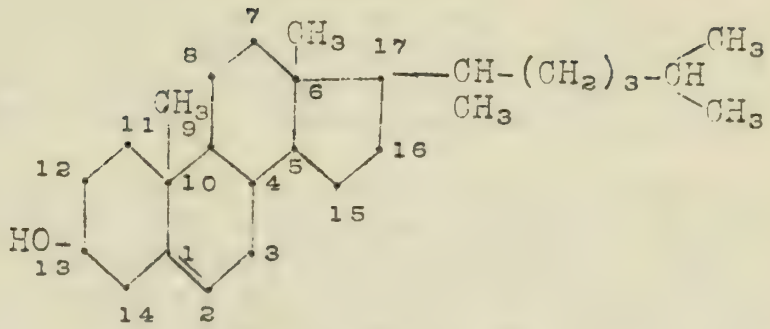
pinene

III 

Syst. Ali. II C_7

(trimethyl 3.7.7)
gephyro 2.7.6
cyclo hexene-3.

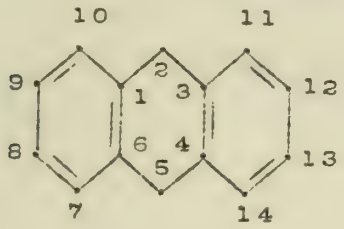
cholesterol

IV 

Syst. Ali. IV C_{17}

[dimethyl-6.10 (dimetho$_{1\ 5}$hexyl)-17,
hydroxy-13] bigephyro | 10.11.12.13.14.1 |
| 5.15.16.17.6 |
bicyclo-4.9 decene-1.

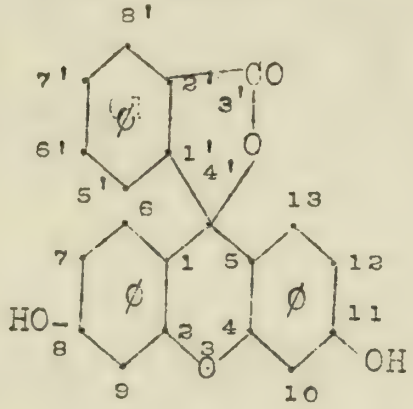
9,10-dihydroanthracene

V. 

Syst. Ali. I, Aro. II C_{14}

bigephyro | Ø 6.7.8.9.10.1 |
| Ø 3.11.12.13.14.4 |
cyclohexane

fluoresceine

VI. 

Syst. Ali. II, Aro. III $C_7O>C<C_{12}O$

(dihydroxy 8.11)
Trigephyro | Ø 1.6...2 |
| Ø 4.10...5 |
| Ø 1'.5'...2' |
[cyclo oxa 4' tetracarbanone 3']
spiro [cyclo oxa 3 penta carbane]

Summary.--The authors claim that the system will name any polycyclic compound in a single way and is capable of unlimited extension.

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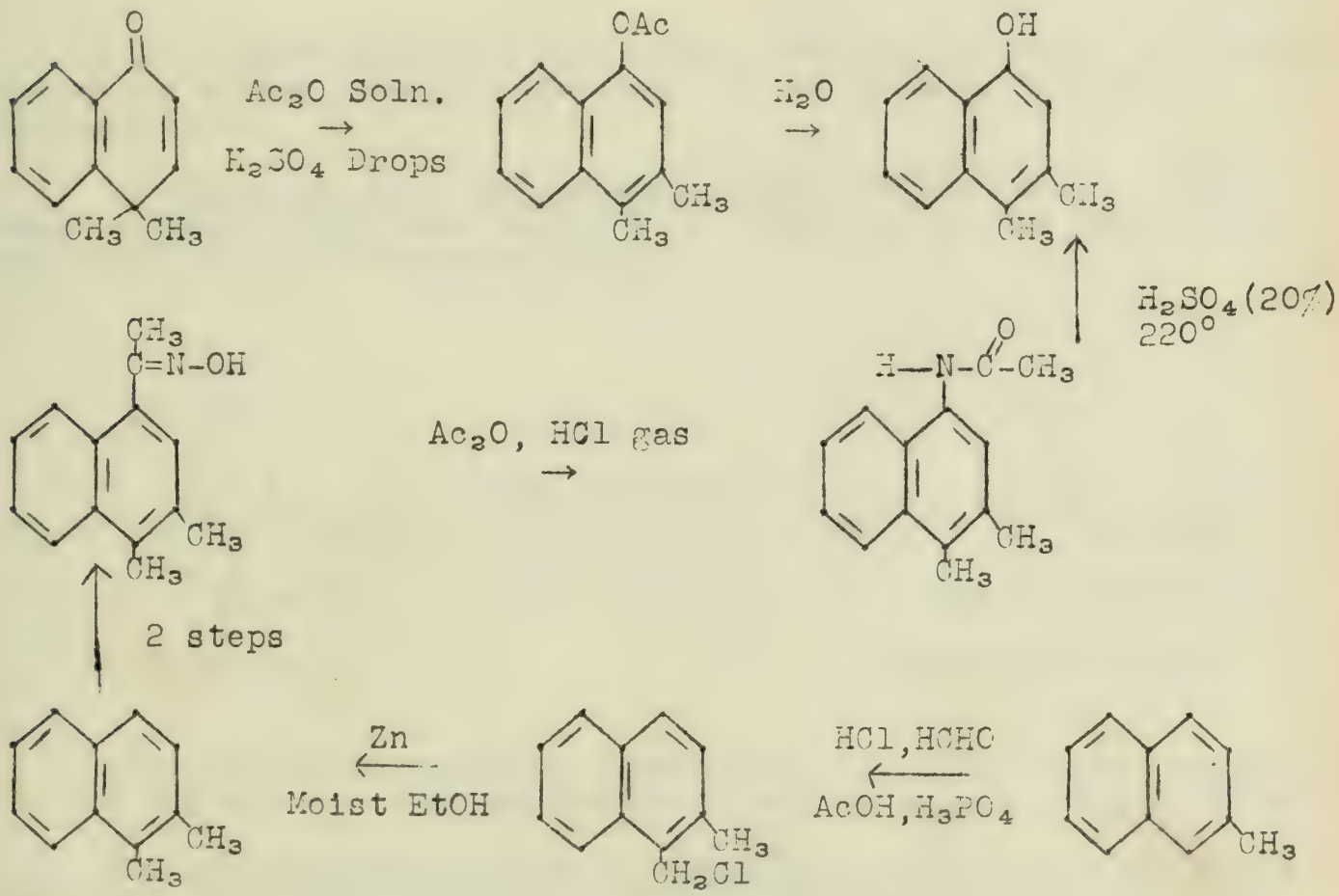
Reported by Nils K. Nelson
December 19, 1947

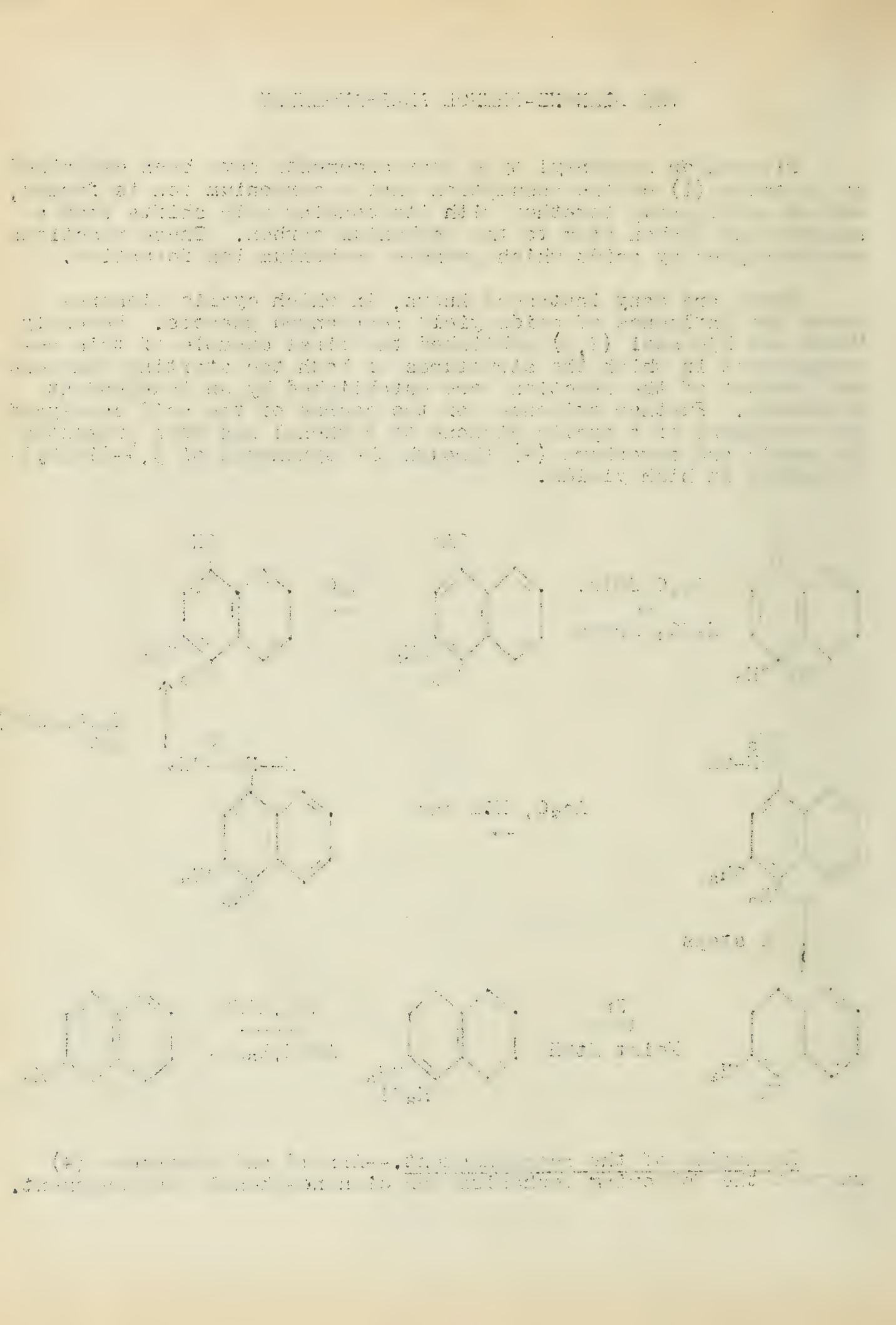
THE DIENONE-PHENOL REARRANGEMENT

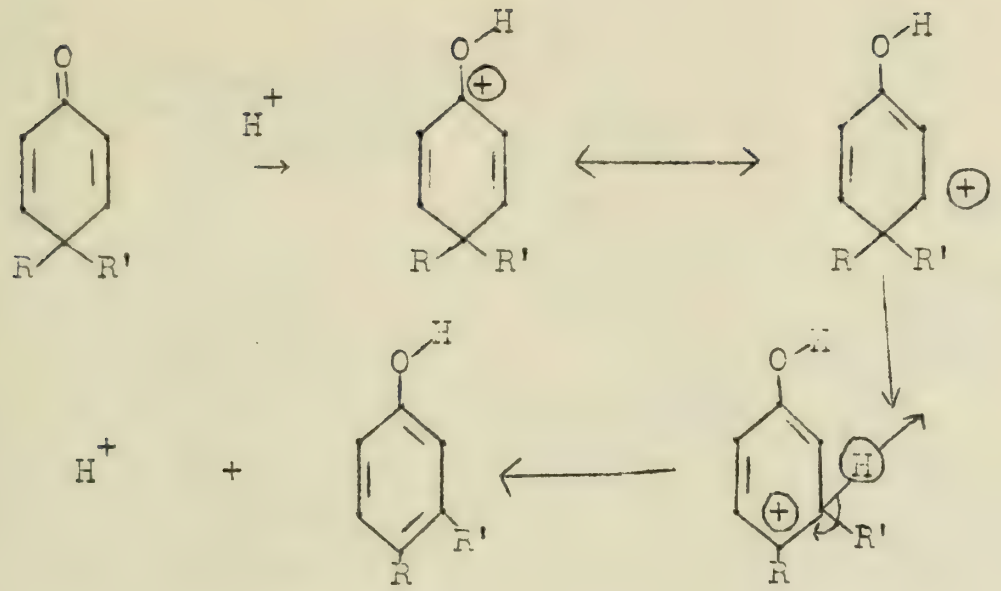
Pinacol or neopentyl type rearrangements have been explained by Whitmore (1) on the assumption that a carbonium ion is formed, and an alkyl group together with its bonding pair shifts from a neighboring carbon atom to the carbonium carbon. These reactions are catalyzed by acids which promote carbonium ion formation.

There are many instances known, in which cyclic dienones under the influence of acids yield rearranged phenols. Recently Wilds and Djerassi (2,3) published the first example of this rearrangement in which the structures of both the starting compound and product of the reaction were established by an independent synthesis. Further evidence for the course of the acid catalyzed rearrangement of a cyclic dienone to a phenol has been presented by Arnold and coworkers (4) through the synthesis of 3,4-dialkyl-1-napthol in high yields.



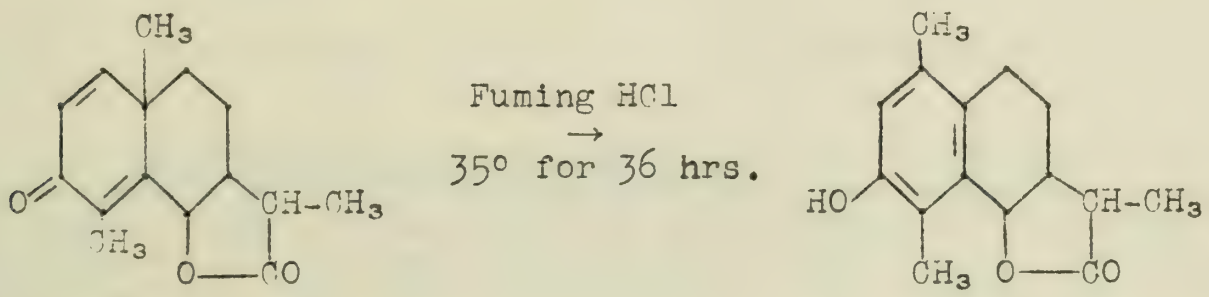
Mechanism of the rearrangement.--Arnold and coworkers (4) suggest the following mechanism for dienone-phenol rearrangement.





Both Arnold and Wilds (3) agree that the following rearrangements are mechanistically the same as the Dienone-Phenol rearrangement.

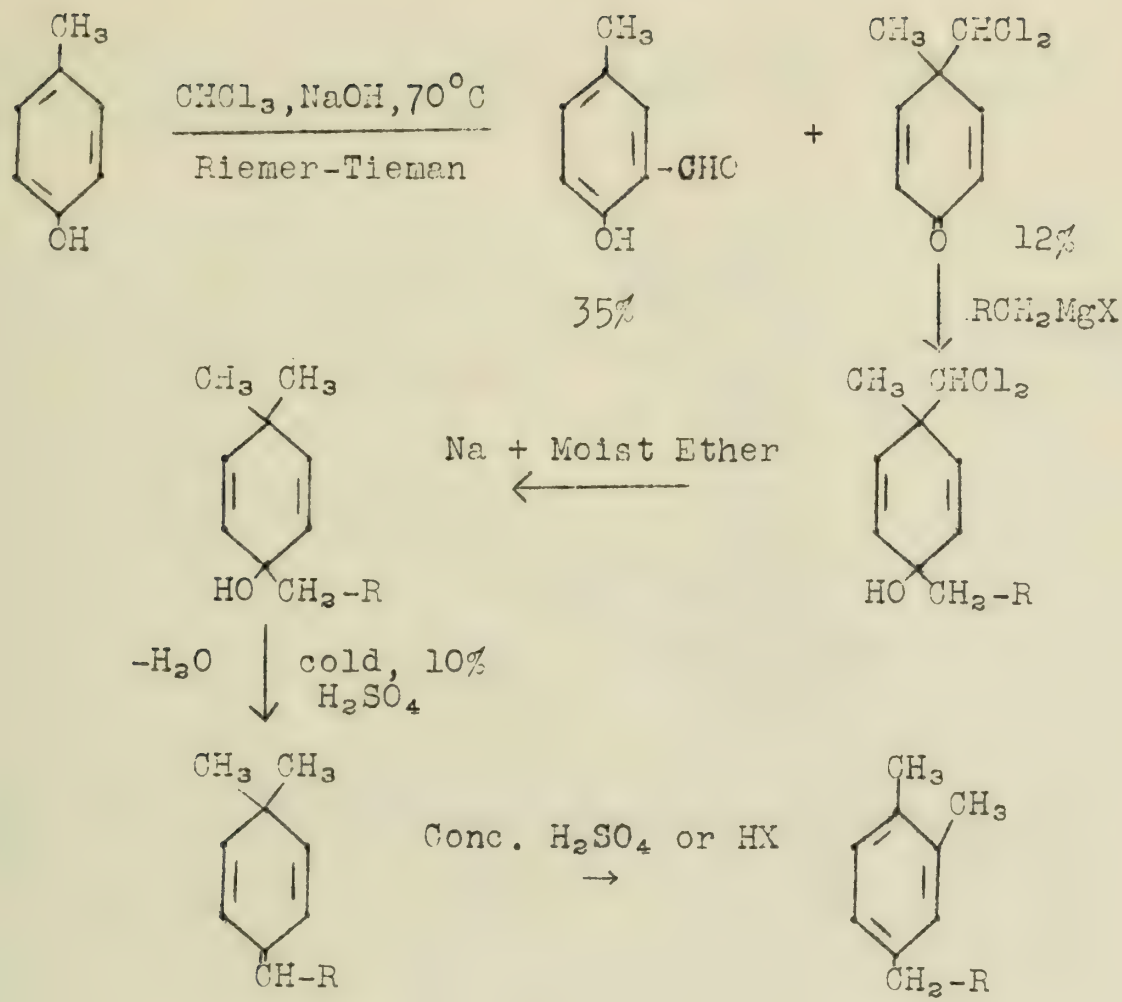
(a) Santonin into desmotroposantonin.--This is a well-known rearrangement which was observed by Clemo (5) in the conversion of santonin to desmotroposantonin.



Santonin desmotroposantonin

Also the rearrangements observed by Inhoffen and coworkers (6) in the cholestanone and androstenone series are of similar nature.

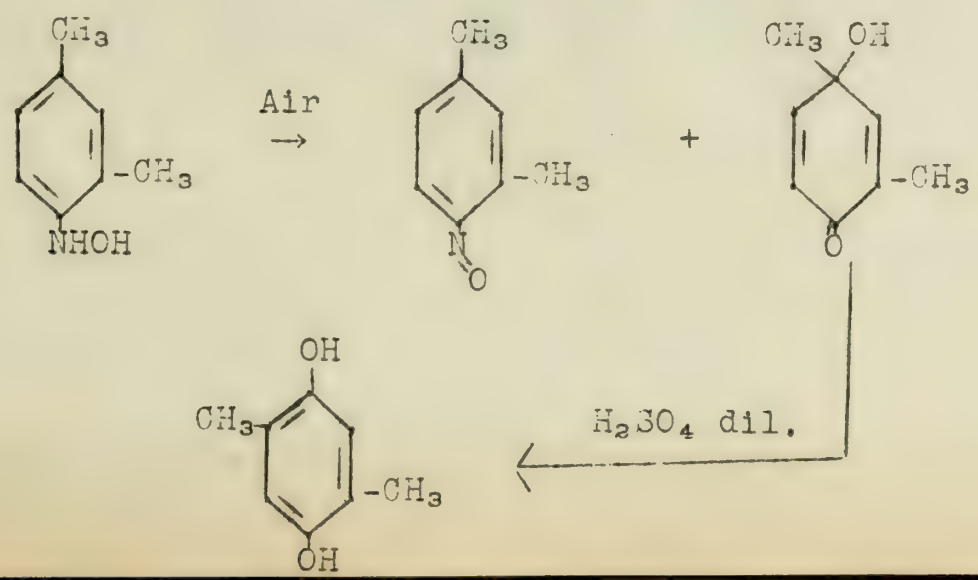
(b) Semibenzenes into alkyl-benzenes.--Rearrangement of semibenzenes into alkyl-benzenes has been studied in some detail by v.Auwers and Ziegler (7). Semibenzenes are unstable compounds which tend to polymerize by heating or even by keeping for a few days, but in the presence of acids they rearrange into alkyl-benzenes.



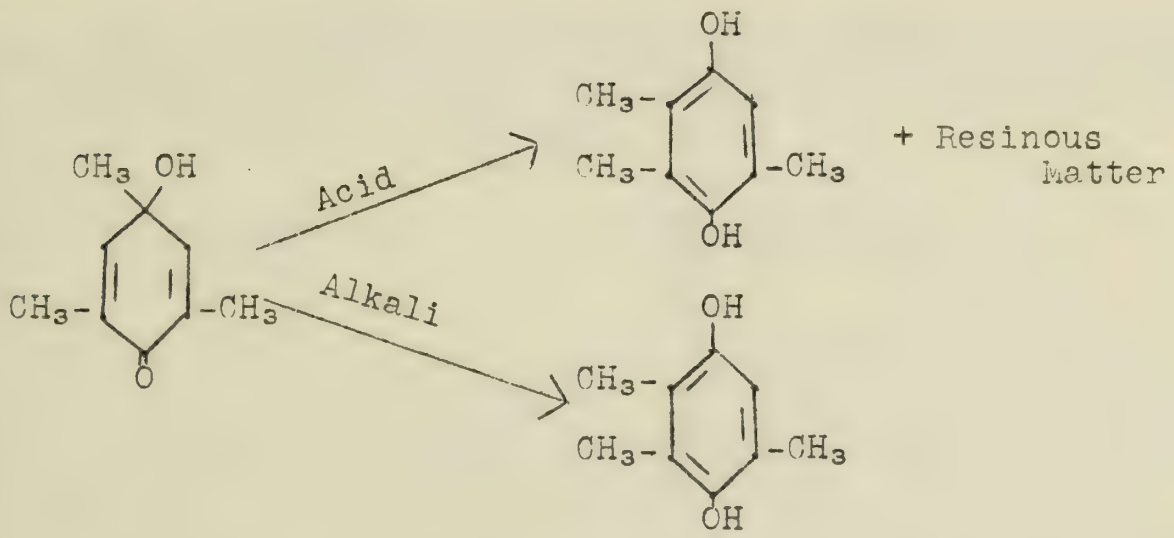
Semibenzene

Alkylbenzene

(c) Quinols into hydroquinones.--Wilds (3) includes quinol rearrangement in the dienone-phenol type rearrangement but Arnold (4) has not made any reference to this inclusion. Bamberger and coworkers (8,9) obtained quinols by the oxidation of corresponding hydroxylamines. By acid catalysis the quinols rearrange into hydroquinones.



However, mesityl quinol (8) undergoes rearrangement in alkaline as well as acidic medium.



The mechanism of the alkali catalyzed reaction is not known.

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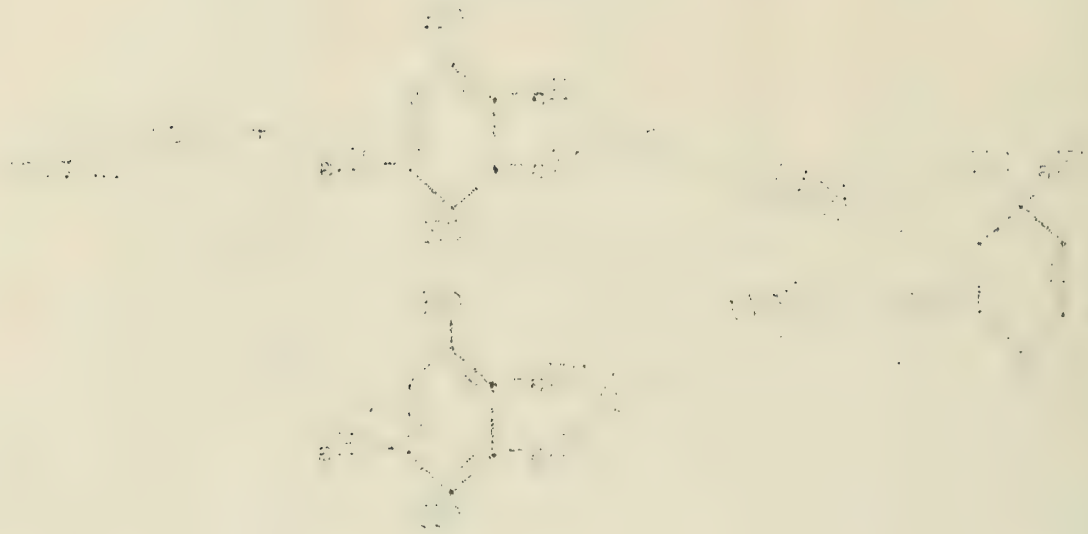
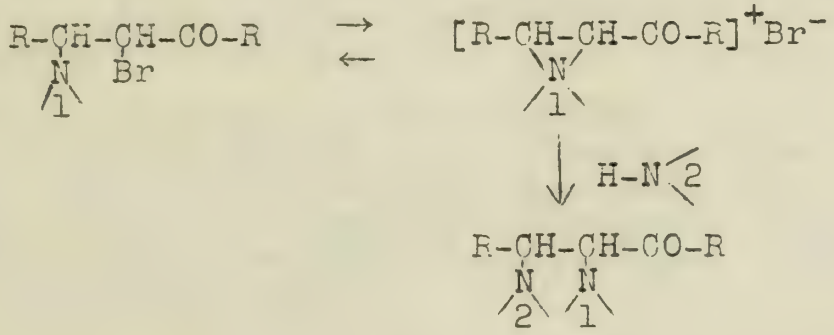
Reported by Akhlaq R. Kidwai
December 19, 1947



α,β-DIAMINO KETONES

α-Bromo-α,β-unsaturated ketones react with primary and secondary amines to give mixed α,β-diamino ketones. The preparation of many specific mixed diamino ketones of possible chemotherapeutic interest has thus been made possible.

I. Reactions of Heterocyclic Secondary Amines with α-Bromo-β-Amino Ketones.--Heterocyclic secondary amines react readily with α-bromo-β-amino ketones to give the expected α,β-diamino ketones by the following reaction:



In all cases the yields are highest when the amine used is a weaker base than the amine of the α-bromo-β-amino ketone. For example, α-bromo-β-morpholinobenzylacetone reacts with tetrahydroquinoline (weaker base than morpholine) to give good yields of the expected α-morpholino-β-tetrahydroquinolinobenzylacetone. The structure of this compound was established by hydrolysis to give α-morpholinoacetone, isolated as its oxime. This same bromo amino ketone reacts in dry ether with piperidine (stronger base than morpholine) to give very poor yields of α-morpholino-β-piperidinobenzylacetone.

The yields varied from 15 to 50% in more reactions described.

II. Reactions of Thalline(tetrahydro-6-methoxyquinoline) and Open Chain Secondary Amines with α-Bromo-β-Amino Ketones.--β-Piperidino- and β-morpholino-α-bromobenzylacetophenone and the corresponding benzylacetones react readily with thalline to give good yields of the mixed diamino ketones (40 to 85%). However, when open chain secondary amines are used (such as N-methylbenzylamine) in place of thalline, poor yields of the mixed diamino ketones result and the major portion of the reaction proceeds to give the colored α-piperidinobenzalacetophenone and α-piperidinobenzalacetone.

The open chain secondary amines used were all weaker bases than the amine in the bromo amino ketone so the difference in their reactions as compared with the reactions of heterocyclic secondary amines must be due to the relative steric effects of these two types of amines. The formation of mixed amino ketone from the quaternary ammonium salt results from an attack of the amine at the β-carbon atom. Cromwell believes that open chain secondary

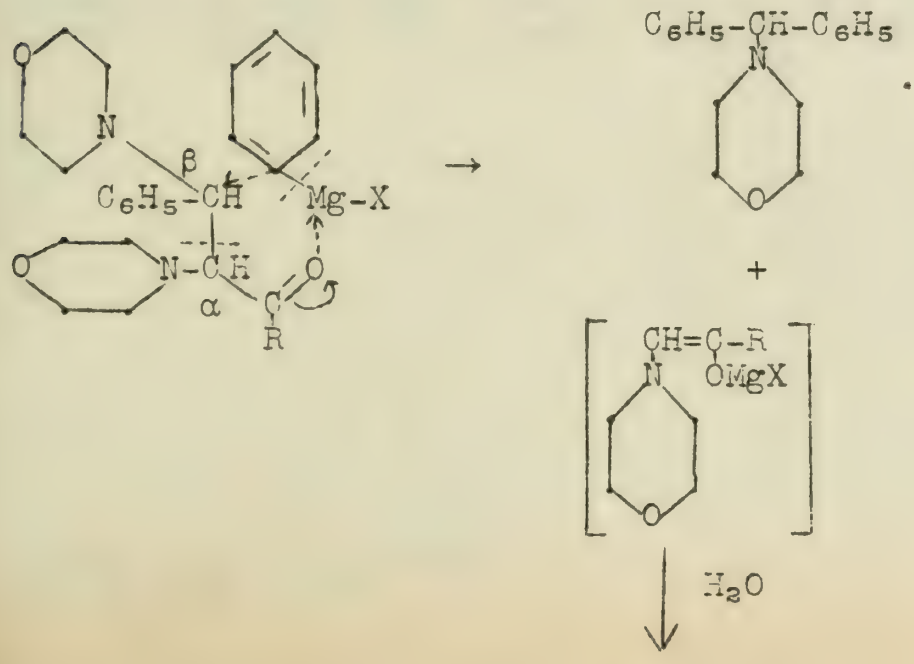
amines might be more hindered in their approach to the β-carbon atom than heterocyclic secondary amines; and also that the basic strength of the amine is a controlling factor. Thus the low yields resulting when N-methyl-ethanolamine is used is probably due to a combination of the steric factor and the considerable strength of this base.

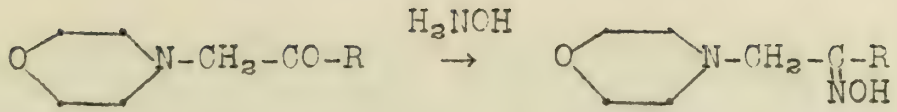
III. Reaction of 8-Amino-6-Methoxy Quinoline with α-Bromo-β-Amino Ketones.--Various α-bromo-β-amino ketones and 8-amino-6-methoxy quinoline(plasmoquin) have been allowed to react with each other with the hope that antimalarial activity might be enhanced. A series of the desired mixed diamino ketones with the 8-amino-6-methoxy quinoline in the β-position were formed in good yields.

Plasmoquin base was not strong enough to react with α,β-dibromobenzylacetone or with α-bromobenzalacetone under the usual conditions. Unsuccessful attempts were also made to introduce two other pharmacologically important amino groups into such molecules by treating α-bromo-β-morpholinobenzylacetone with 2-amino pyridine and with 2-amino pyrimidine.

IV. Addition and Cleavage with Grignard Reagents.--α,β-Dimorpholinobenzylacetone reacts with phenyl magnesium bromide to give a fair yield of the expected carbinol, 2,4-diphenyl-3,4-dimorpholinobutanol-2, and the corresponding α,β-dimorpholinobenzylacetophenone reacts with methyl magnesium iodide to give the same carbinol but in very low yields. This is typical of Grignard reactions where the increased size of certain groups alter the course of the normal reaction. Thus, when α,β-dimorpholinobenzylacetophenone reacts with phenyl magnesium bromide only a 4% yield of the expected carbinol results and large amounts of lower molecular weight cleavage products are formed.

A mechanism for this unexpected cleavage may be postulated as follows:





The Grignard reagent is attracted in the normal manner, as a result of the nucleophilic nature of the carbonyl oxygen toward the electrophilic metal portion of the reagent. Since the "normal" approach of the nucleophilic organic portion of the reagent toward the electrophilic carbonyl carbon atom is sterically hindered by large groups on both sides in some of these molecules, an alternative electrophilic carbon atom becomes a competitive reactive center. As is indicated in the diagram, the β-carbon is electrophilic and the organic portion of the reagent may approach it via a quasi-six membered ring. The α-carbon-β-carbon bond has been shown to be weak because of the presence of several electron attracting groups and thus susceptible to cleavage by dilute acids. As the organic portion of the Grignard reagent approaches the β-carbon atom, the formal bonds are broken, and the electrons shifted to give the indicated products which are stable substances. This cleavage mechanism would not require actual ionization of the Grignard reagent.

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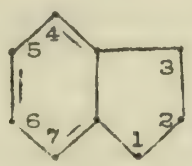
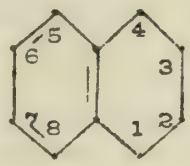
Reported by D. J. Mann
December 19, 1947

THE MILLS-NIXON EFFECT

From a theoretical examination of the bond angles existing around a carbon-carbon double bond, Mills and Nixon (1) postulated that there should be a fixation of the double bonds in a benzene nucleus when that nucleus is fused through adjacent carbon atoms to a five- or six-membered saturated ring. Thus in hydrindene (I) and in tetralin (II) one Kekulé form of the benzene nucleus would predominate over the other according to the following formulas:



I



II

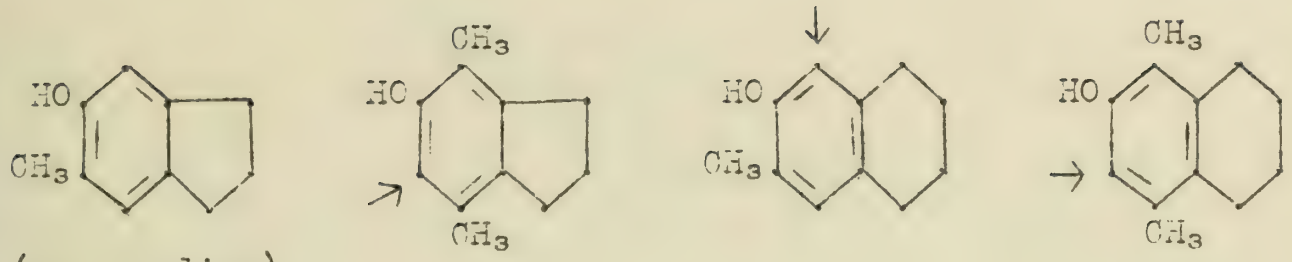
In support of this theory the following evidence was submitted. The reactions cited are those which are believed to involve substitution at the ortho position separated from the activating group by a double bond and thus are taken as an indication of the position of the double bonds in the benzene nucleus. 6-Hydroxytetralin is brominated and couples with diazotized aniline in the 5-position while similar reactions with 5-acetylhydrindene and 5-hydroxyhydrindene take place in the 6-position. In the coupling of 5-hydroxyhydrindene with diazotized aniline or p-nitroaniline a small amount of the 4-isomer is obtained. In the following compounds the position of the unsaturation is taken as an indication of the inability of a five-membered ring to accommodate a double bond:


$-CH(CO_2Et)_2$


$=C(CO_2Et)_2$

The same considerations are involved in the enolizability of certain β-keto esters; 2-carbethoxycyclopentanone, 4.5%; 2-carbethoxycyclohexanone, 76%; 3-carbethoxy-2-tetralone, 76%; 2-carbethoxy-1-tetralone, 100%; 2,3-dicarbethoxycyclopentanone, 10%; 2-carbethoxy-6-methylcyclohexanone, 40% (2,3). A study of the dipole moments of 5,6-dibromohydrindene and 6,7-dibromotetralin (4) has led to the conclusion that fixation occurs in hydrindene but not in tetralin.

Fieser and Lothrop (5,6) have made a detailed study of the diazo coupling of substituted 5-hydroxyhydrindenes and 6-hydroxytetralins. In the following formulas the arrows indicate the position of major coupling:



(no coupling)

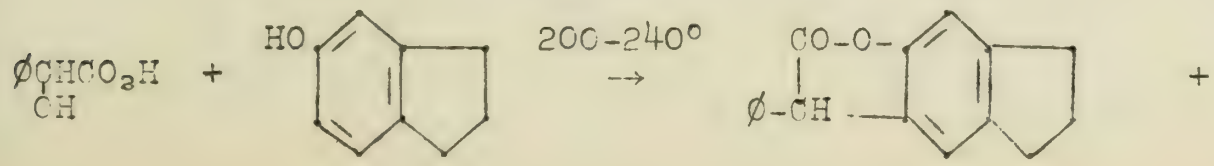
McLeish and Campbell (7,8) determined the rate of removal of bromine by piperidine from certain bromo-nitro compounds. The bromine atom should be highly reactive if separated from the nitro group by a double bond. The results are given in Table II which indicate the hydrindene to have a fixed bond structure while one for tetralin is impossible.

TABLE II

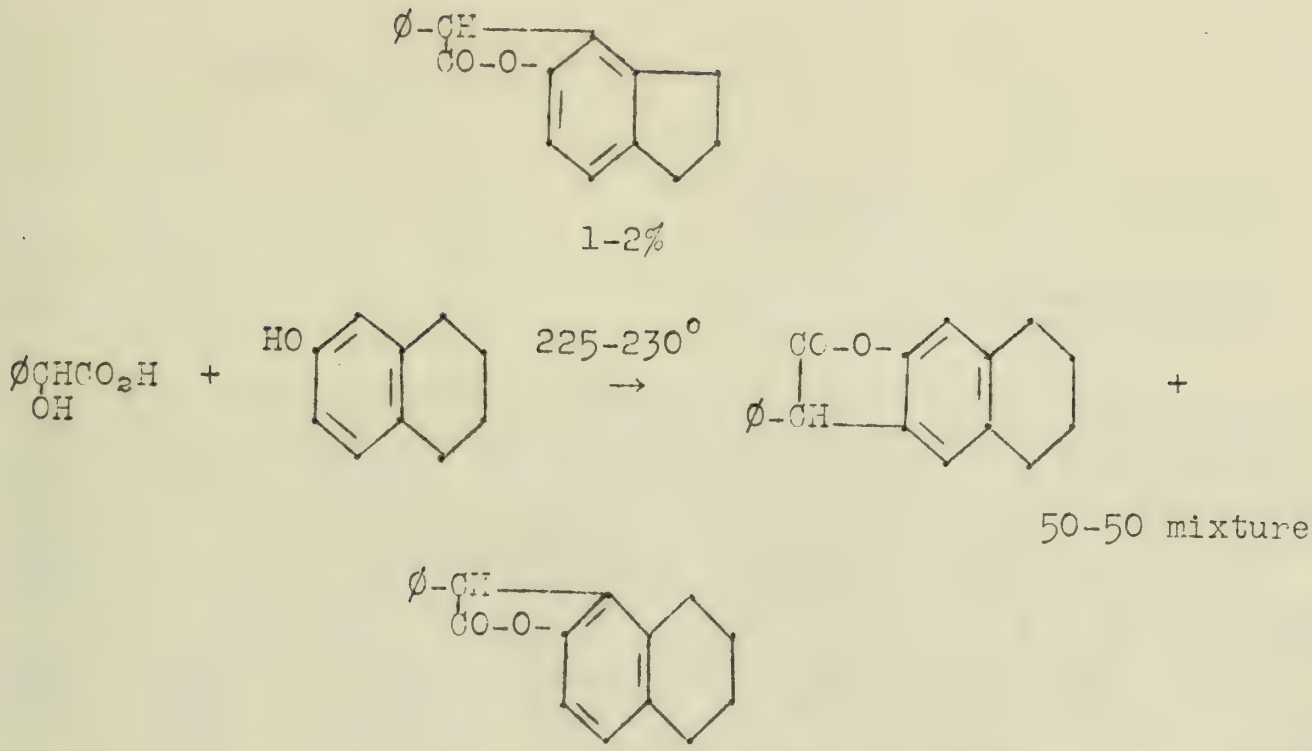
Compound	Per Cent Bromine Removed 0.5 hr.	20 hr.
4-bromo-5-nitrohydrindene	---	<5
5-nitro-6-bromohydrindene	---	72
5-nitro-6-bromotetralin	0	0
6-bromo-7-nitrotetralin	5	51

By a comparison of the extent of chelation of 5-hydroxy-6-acetylhydrindene and 5-hydroxy-4-acetylhydrindene, Baker (9) added confirmatory evidence to the bond fixation in hydrindene derivatives. The former is soluble in benzene and is volatile with steam while the latter is nearly nonvolatile with steam and is difficultly soluble in hydrocarbon solvents. Arnold and Evans (10) investigated the chelation of 5-nitro-6-hydroxyhydrindene and 6-nitro-7-hydroxytetralin and found no evidence in favor of stabilization of the bond arrangements. The Claisen rearrangement of the allyl ethers of certain hydroxyfluorene and hydroxyhydrindene compounds was studied (11,12). No bond fixation in fluorene or hydrindene was indicated.

Arventi (13) investigated the formation of lactones between mandelic acid and 5-hydroxyhydrindene and 6-hydroxytetralin. These reactions indicate a fixation in hydrindene but not in tetralin.

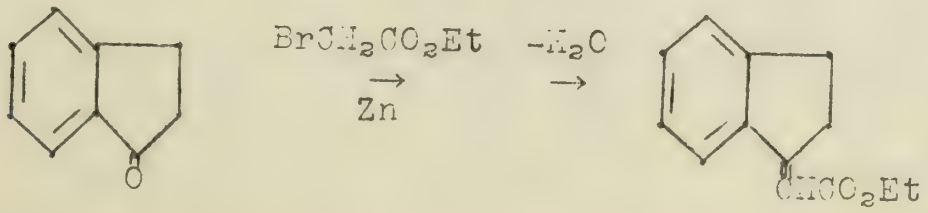


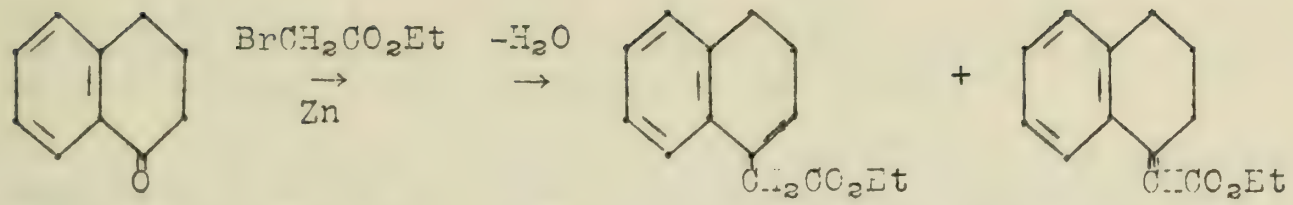
50-55%



Long and Fieser (14) have studied the products of ozonolysis of hydrindene. If the bonds are fixed in the positions predicted by Mills and Nixon the products should be glyoxal and cyclopentadione-1,2. The compounds isolated were glyoxal and succinic acid, the succinic acid resulting from further oxidation of the cyclic diketone.

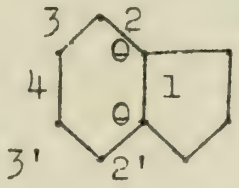
Arnold and Zaugg (15) measured the oxidation-reduction potentials of o-xyloquinone, 4,7-hydrindene quinone and 1,2,3,4-tetrahydronaphthoquinone in the hope of demonstrating the fixation of bonds in the hydrindene molecule. It was reasoned that 4,7-hydrindene quinone should give a higher value for the oxidation-reduction potential because of its tendency to relieve the strain produced by the double bond in the five-membered ring. Measurements of E_0 for these three quinones indicate a partial stabilization of the predicted Kekulé form for hydrindene. Buu-Hoi and Cagniant (3,16) added further proof to the theory of Mills and Nixon. By the following reactions they demonstrated the seeming reluctance of the five-membered ring of hydrindene to accommodate a double bond:



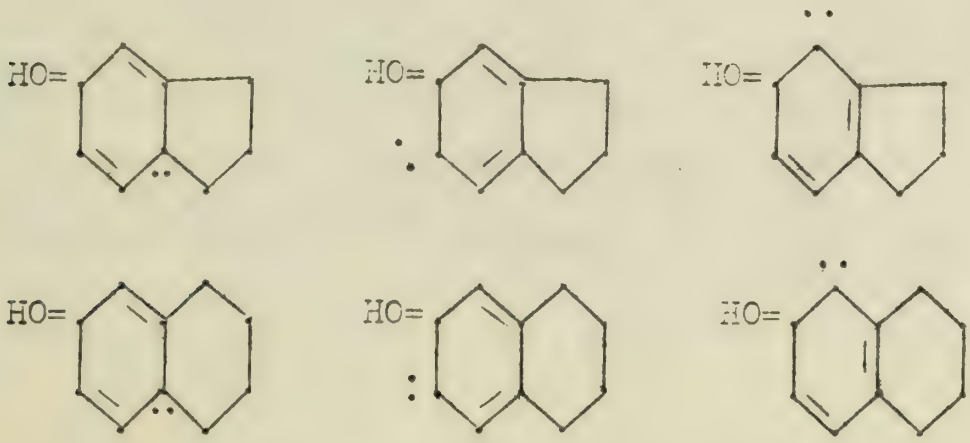


(small amount)

The physical evidence which has accummulated on this subject indicates no bond fixation in hydrindene or tetralin. Sutton and Pauling (17) examined the Mills-Nixon effect by a wave mechanical treatment and found that the benzene nucleus retains the greater part of its stabilizing resonance energy when fused to a saturated side ring. Similar results were obtained by Kossiakoff and Springall (18) from an electron-diffraction study. An investigation of molecular orbitals by Longuet-Higgins and Coulson (19) gave a result in direct opposition to the Mills-Nixon theory. Their study indicates a tendency for the angles θ (figure below) to be opened resulting in a compression of bond 1 and an extension of bond 4.



Pullman (20) criticized the use of substitution reactions to fix the location of bonds in an aromatic nucleus. Due to the introduction of a hydroxyl group into the molecule the following mesomeric forms are suggested for 5-hydroxyhydrindene and 6-hydroxytetralin.



It is suggested that ease of substitution is not due to the preponderance of a given type of Kekulé structure but is a function of the charges in various parts of the nucleus.

A question was raised as to the validity of the original assumptions of Mills and Nixon when Thompson (21) showed that the bond angles in ethylene are 118° between the free bonds and 121° between any single free bond and the plane of the double bond and when Pauling and Brochway (22) found the bonds in tetramethylethylene to be 120°.

All of this evidence demonstrates clearly that the theory of Mills and Nixon is still an unsettled question. The physical evidence indicates that no stabilization of the suggested Kekulé form exists, yet this leaves us seeking an explanation for the chemical behavior of substituted hydrindene and tetralin molecules.

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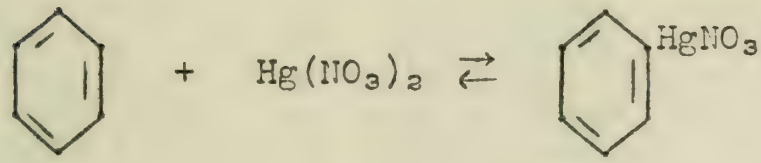
Reported by William H. Libby
December 19, 1947

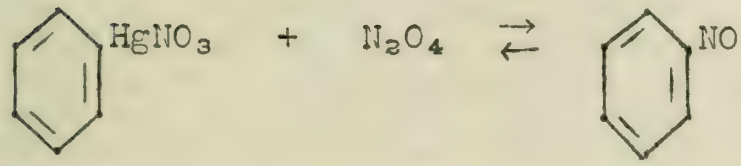
THE OXYNITRATION OF BENZENE

I. Introduction.--It has been found that benzene can be oxidized to dinitrophenol or picric acid by a nitric acid solution of mercuric nitrate. This process was first described in a patent issued to Wolffenstein and Boeters in 1908 and has since been known as the oxynitration process. During the recent war the process became of general interest and as a result of research initiated by the NDRC the overall yield in the conversion of benzene into dinitrophenol was increased to about 85%.

II. General Mechanism.--The general mechanism of the reaction has been established beyond reasonable doubt, the process having been found to proceed in the following steps:

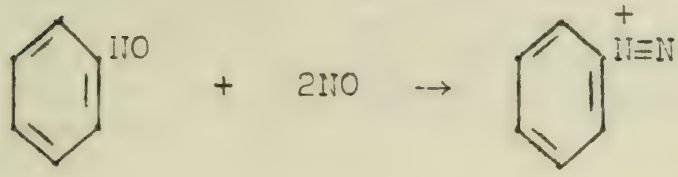


(1)

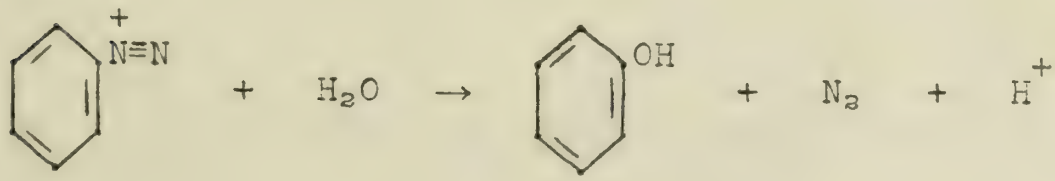


(2)

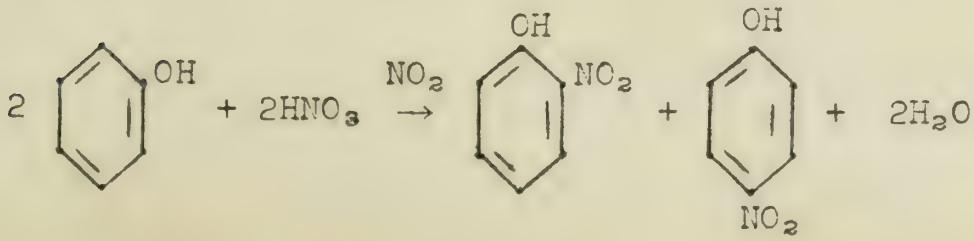
The nitrosobenzene formed can now react in two ways. In solutions with a high nitrite concentration and a low nitric acid concentration, the reaction is as follows:



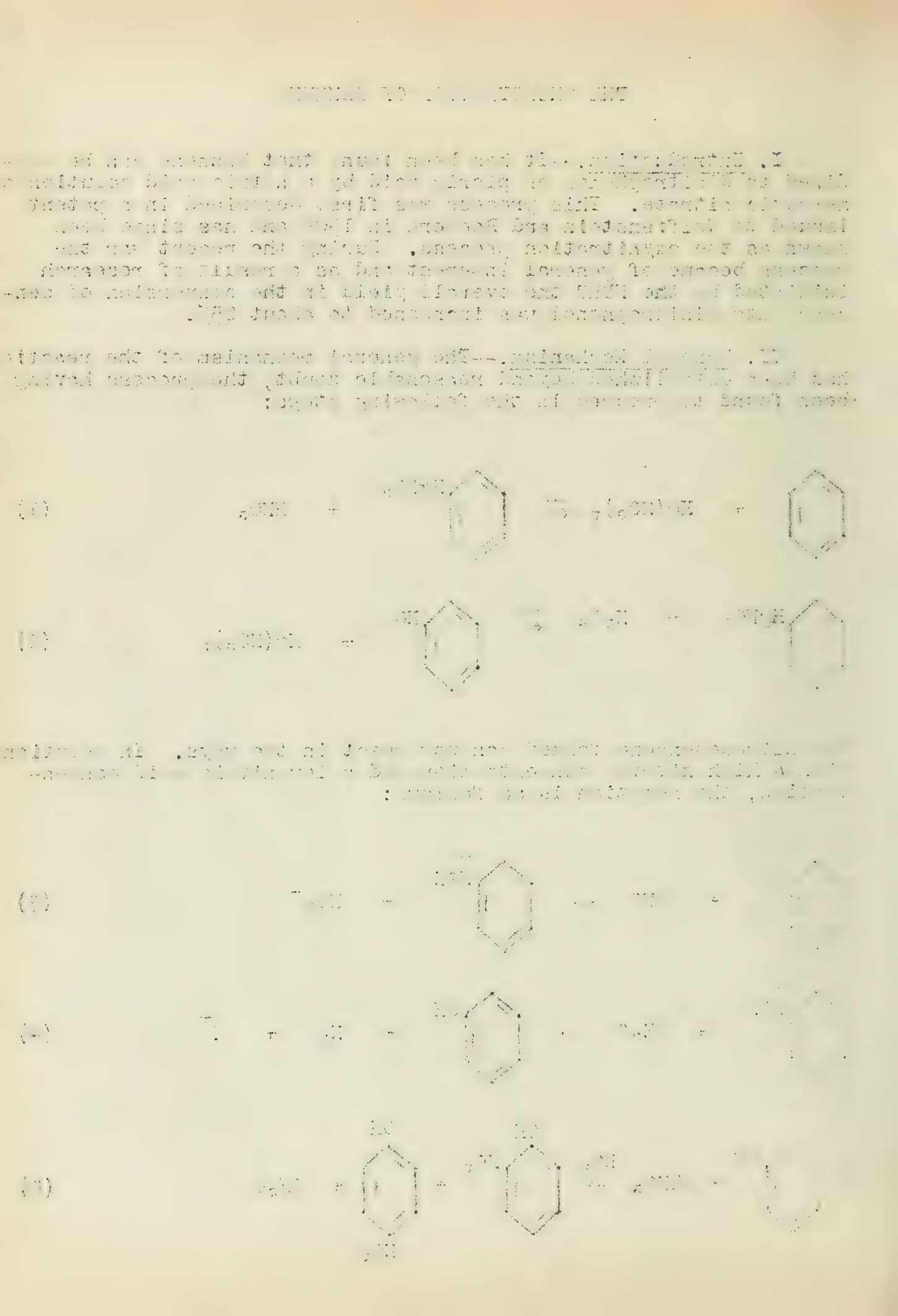
(3)



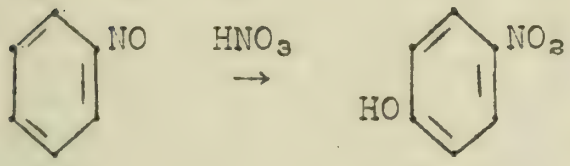
(4)



(5)



However, with a low nitrite concentration and a high nitric acid concentration a process involving oxidation and "rearrangement" occurs:

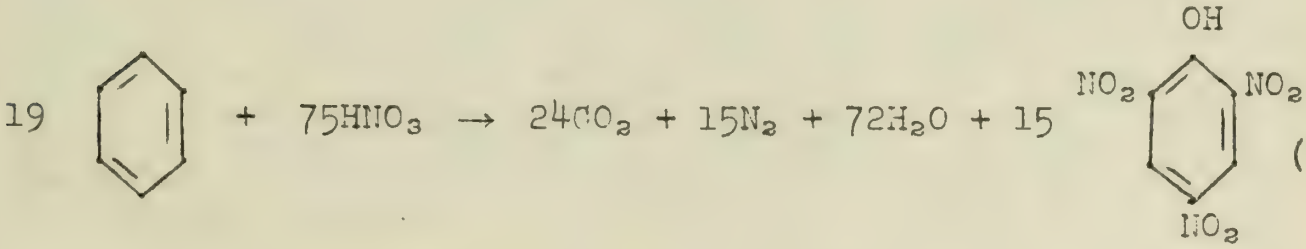


(6)

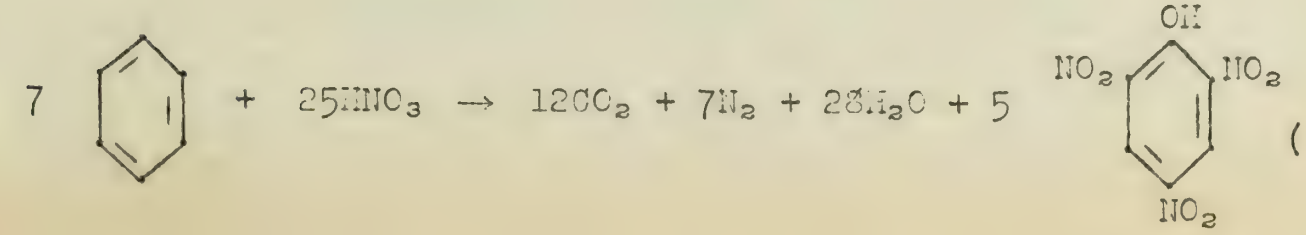
The mononitrophenol then undergoes nitration to the di- and trinitro derivatives in the usual manner.

Proof of the above mechanism included the isolation of several of the postulated intermediates, such as the phenylmercuric ion, and phenyldiazonium nitrate. Evidence for the formation of mononitrophenols was also obtained, and both nitrogen and nitrobenzene were found to be present among the reaction products. Of more importance was a consideration of the rates of the proposed steps in the reaction under widely different conditions of temperature and reagent concentration. Moreover, the rates of several side reactions were investigated and the amount of interference caused by each was approximated. Such rate studies showed the postulated mechanism to be in agreement with the known facts.

III. Stoichiometry of the Reaction.--Since the amounts of reagent consumed in this reaction were of practical importance in its application, considerable attention was given to the stoichiometry involved. Two different interpretations of this aspect of the reaction have been advanced. In both, the assumption that the necessary nitrogen oxides can be supplied only by a reduction of nitric acid was made. Carmack has pointed out that when oxynitration occurs by a mechanism involving a diazonium salt intermediate two stoichiometric representations of the reaction are possible:

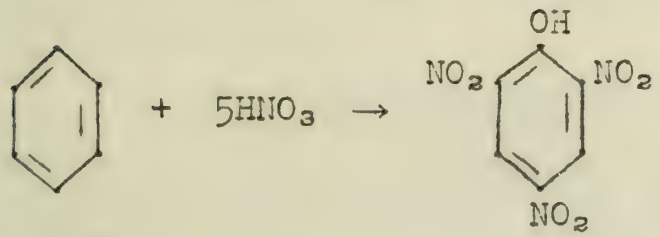


(7)

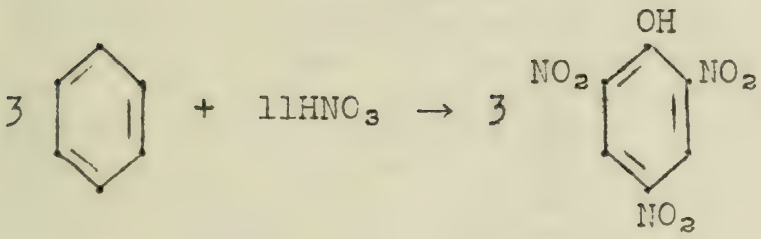


(8)

Equation (7) is based on the assumption that either benzene or nitrosobenzene is oxidized to carbon dioxide by nitric acid and the diazotization which follows this oxidation consumes all of the nitrous acid which is formed. In equation (8) it is assumed that the oxidation of phenol furnishes the necessary nitrous acid. The maximum yield which can be expected from equation (7), based on the amount of benzene used, is 79% in contrast to the 71% theoretically obtainable from the reaction as represented by equation (8). On the other hand, if the reaction were to proceed according to either equation (9) or (10) the theoretical yield for picric acid would be 100%.



$$+ \; 5HNO_3 \rightarrow \; + \; 4H_2O \; + \; 2NO_2 \qquad (9)$$



$$+ \; 11HNO_3 \rightarrow 3 \; + \; 10H_2O + 2NO \qquad (10)$$

These two latter equations do not involve the various intermediates which have been postulated for the reaction. The stoichiometric equations proposed for the formation of dinitrophenol rather than picric acid are similar to equations (7) and (8).

IV. The Mercuration of Benzene.--The rates and equilibria of the mercuration process were determined by titrating aliquot portions of the reaction mixture with thiocyanate. The equilibrium between the mercuric nitrate and the benzene was found to be representable by equation (1) and the rate of mercuration was observed to increase markedly with an increase in hydrogen ion concentration. Because the rate of the oxynitration process itself varies directly with the amount of nitric acid present, the rates of oxynitration and mercuration were found to closely parallel one another. Moreover, the rate of mercuration was shown to be independent of the source of hydrogen ion and acid catalysis of the process was assumed.

V. The Diazotization Reactions.--Phenyldiazonium nitrate concentration was determined as follows: Phenylmercuric nitrate or nitrosobenzene was dissolved in dilute nitric acid and both sodium nitrite and a coupling agent, such as R salt, were added. The dye which formed was measured colorimetrically. Applying these quantitative data to studies of the reaction rate indicated that phenylmercuric nitrate must first be converted into nitrosobenzene

and only subsequently into the diazonium compound. The rate of diazotization of nitrosobenzene was indicated as being independent of the nitric acid concentration while an increase in the nitric acid concentration was found to greatly increase the rate of conversion of the phenylmercuric nitrate into nitrosobenzene. However, the rate of diazotization of the nitrosobenzene seemed to be much more dependent on the total nitrite concentration than was the rate of conversion of the phenylmercuric nitrate into nitrosobenzene. In dilute solutions of nitric acid the conversion of both phenylmercuric nitrate and nitrosobenzene into phenyldiazonium nitrate appeared to be essentially complete. This has been found to be true even when a moderate concentration of nitrite was present in the acid.

VI. The "Rearrangement".--In concentrated solutions of nitric acid, phenylmercuric nitrate is readily converted into nitrosobenzene. The nitrosobenzene, however, is unstable in the presence of the concentrated acid, and is converted at once into a nitrated phenol derivative. This conversion was found to proceed not through the diazonium salt or phenol intermediates and is now thought to occur by means of a "rearrangement". The instability of nitrosobenzene in the presence of concentrated nitric acid has been indicated by preparing dinitrophenol from phenylmercuric nitrate under conditions where little or no diazonium compound is produced. Under such conditions, a much higher yield of the dinitrophenol was obtained than could be obtained from phenol nitrated under similar reaction conditions. This was taken as an indication that most of the possible side reactions involving nitrosobenzene had been avoided. Various considerations of the course of the "rearrangement" seem to indicate that the introduction of the hydroxyl group para to the nitroso group is either accompanied or followed by an oxidation of the nitroso group to a nitro group.

VII. Nitration Reactions.--In the oxynitration process, the nitration of phenol, formed as an intermediate in the reaction, has been shown to be catalyzed by the presence of nitrite. The reaction was always accompanied by the formation of an intense red color and a certain amount of insoluble tar of unknown composition. It was determined that at least 20% of any phenol formed during the reaction was destroyed. The reaction, proceeding by way of the diazonium salt intermediate, is thus to be avoided in favor of the reaction involving the "rearrangement", in which little or no phenol is formed. The nitration of the various nitrophenols is also believed to be catalyzed by nitrite, but further nitration of these materials proceeds in a much more efficient manner than the nitration of phenol, the yields often approaching quantitative. Since the mechanism which has been postulated for the reaction does not specify the components of the nitrous-nitric acid system responsible for the catalysis of the nitration, it is still essentially incomplete.

VIII. Side Reactions.--A number of side reactions have been found to complicate the oxynitration of benzene. Some of these

side reactions result in the following:

(1) formation of colored by-products from nitrosobenzene.
(2) formation of nitrobenzene by the direct nitration of the benzene.
(3) formation of ortho and para dinitrobenzenes.
(4) formation of nitrobenzene from nitrosobenzene.

On the basis of the postulated mechanism for the reaction which requires the presence of at least several of the oxides of nitrogen in the reaction mixture numerous attempts to more completely realize this condition by the direct introduction of nitrogen oxides have been tried. Such methods proved to be of no value since in no example was the yield improved. If anything, the direct introduction of such oxides decreased the yield of nitrophenols obtained and increased the extent to which various side reactions proceeded. Similar results were obtained by the introduction of readily oxidizable materials into the reaction mixture. It was, therefore, concluded that high concentrations of nitrogen oxides are detrimental to the yields of the nitrophenolic products produced.

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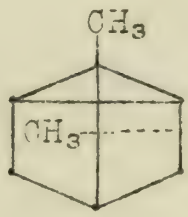
Reported by J. N. Coker
January 9, 1948

STRUCTURE PROOF AND SYNTHESIS OF α-SANTALOL

Introduction.--East Indian sandalwood oil contains about fourteen chemical substances including alcohols, aldehydes, ketones, hydrocarbons and acids. The main bulk, however, is comprised of two sesquiterpene alcohols, α- and β-santalols. Structure proof and synthesis of α-santalol will be discussed in this seminar.

Isolation.--The first necessary step in structure proof, the isolation of a pure sample, is no simple job in the case of the santalols. After saponification of the natural oil, the acids, aldehydes, etc., are removed as derivatives. Then despite the tendency to form a constant boiling mixture the two alcohols are separated by fractional distillation. Guha and Bhattacharyya thus obtained pure α-santalol after twenty-one distillations. The progress of the separation could be followed by the unsaturation number method of Milas and McAlevy. This is possible since the unsaturation number of pure α-santalol is one, while that of β-santalol is two.

Structure Proof.--It was early recognized that a tricyclic system is involved in santalol. Molecular refraction indicated this, while oxidation with $KMnO_4$ gave an acid $C_{12}H_{18}O_2$ which was tricyclic as shown by its stability toward further oxidation. Ozonolysis yielded a tricyclic aldehyde plus hydroxy acetone as the main products. Semmler then ascribed the structure (I) to the acid obtained by permanganate oxidation and called it tricycloekasantalic acid. This structure was postulated after degradation of (I) to nor-tricycloekasantalic acid (II), teresantalic acid (III), teresantalol (IV), teresantalyl chloride (V), and finally teresantalane (VI).

Let R equal 

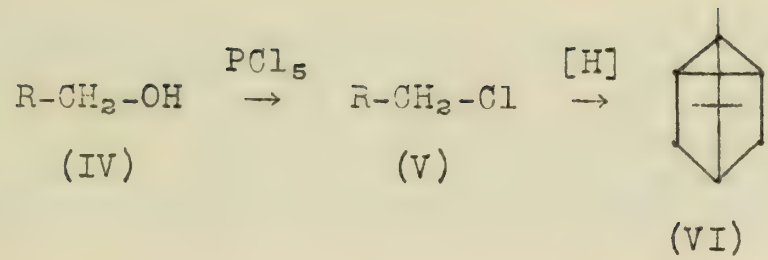
Then α-santalol $\xrightarrow{KMnO_4}$ $R-CH_2-CH_2-COOH$ (I)

$\downarrow$ CH_3OH, H^+

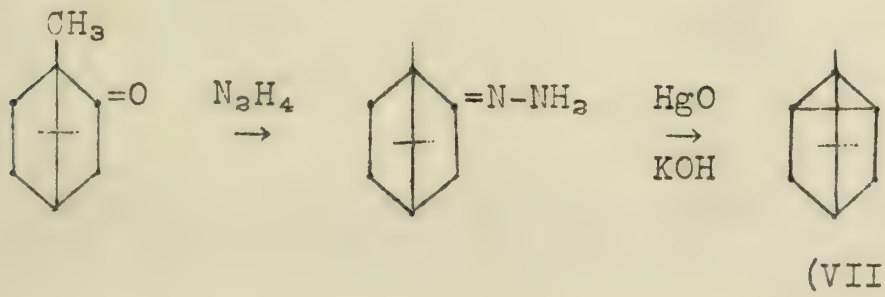
$R-CH_2-CH_2-COOCH_3$ $\xrightarrow[C_2H_5OH]{Na}$ $R-CH_2-CH_2-CH_2OH$ $\xrightarrow{CrO_3}$ $R-CH_2-CH_2-CHO$

$\downarrow$ KOAc, HOAc

$R-CH_2-CH=CH-O-\overset{O}{\overset{\|}{C}}-CH_3$ $\xrightarrow{KMnO_4}$ $R-CH_2-COOH$ (II) $\xrightarrow{5\ steps}$ $R-COOH$ (III) $\xrightarrow{2\ steps}$

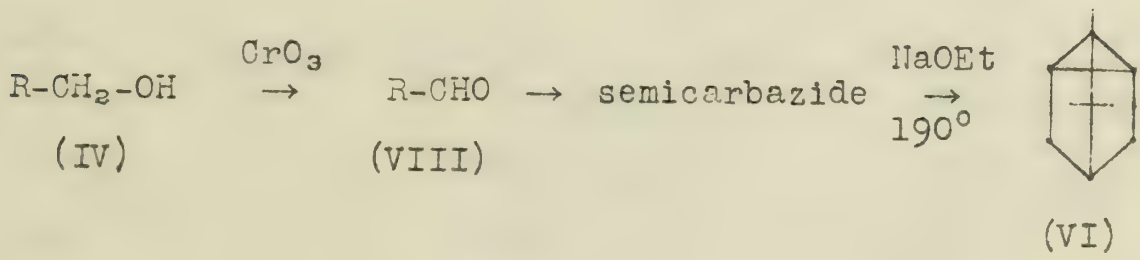


If Semmler's structure for (I) is correct, then teresantalane (VI), should be the same as the tricyclene (VII), prepared by Meerwein and Emster according to the following scheme:

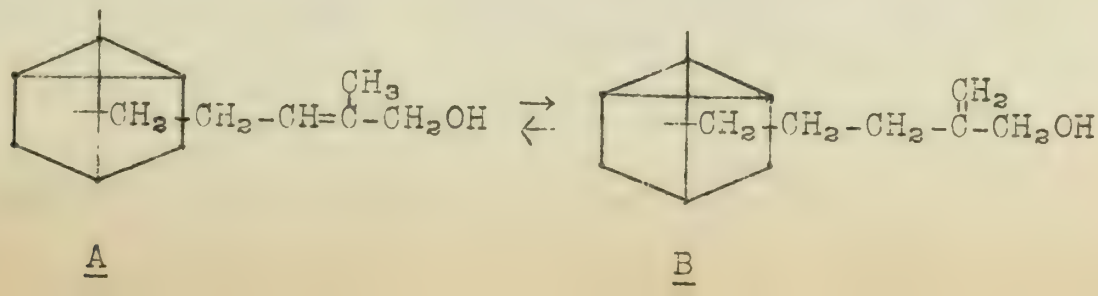


Semmler was unable to show this identity, probably due to his use of PCl_5. This undoubtedly would cause some opening of the cyclopropane ring forming a sufficient amount of chlorinated bicyclic derivatives to prevent accurate identification.

Ruzicka and Liebel did show the identity of teresantalane and tricyclene by converting the teresantalol to teresantalane by a different method which follows:



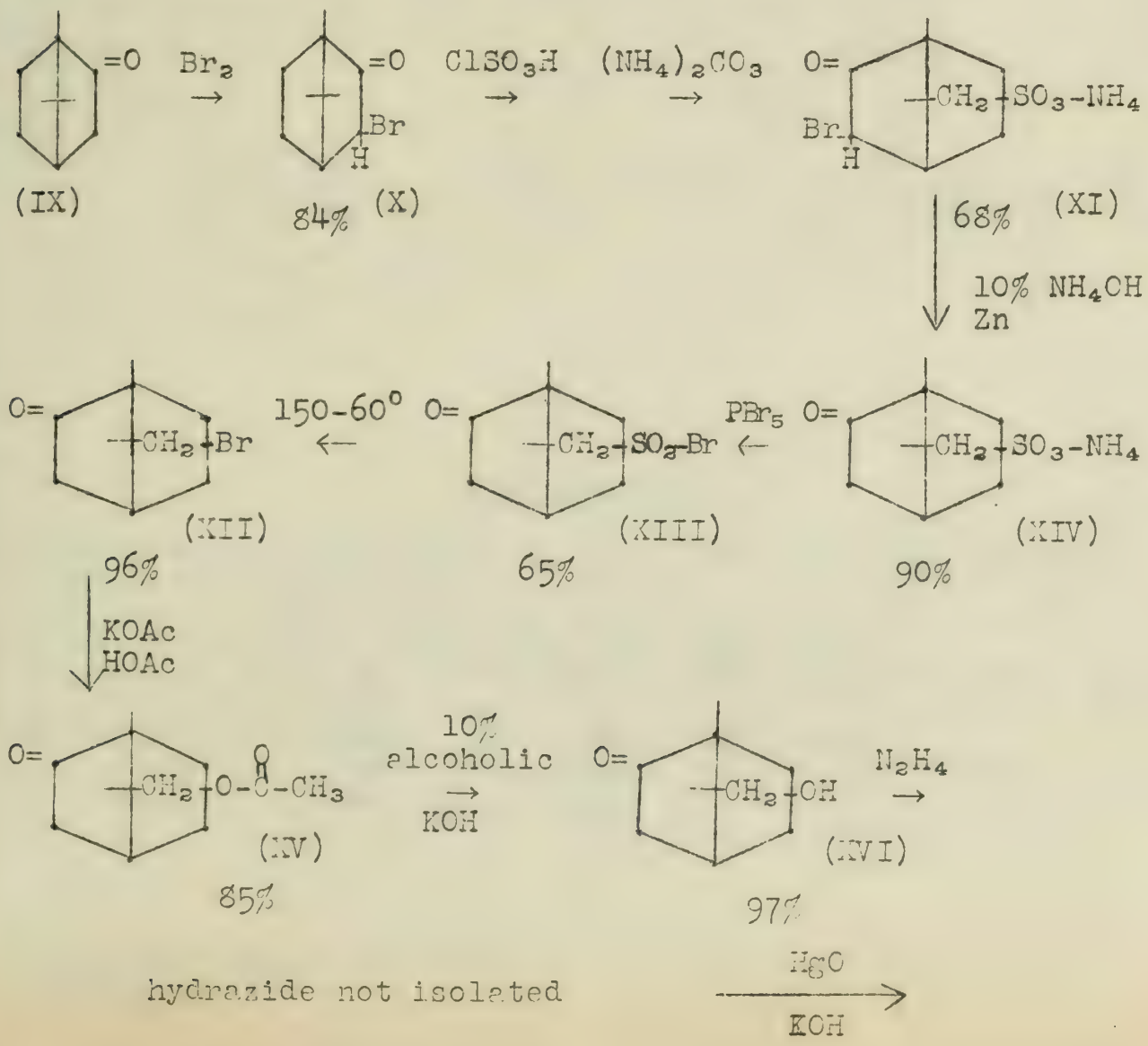
The fact that small amounts of formaldehyde as well as hydroxyacetone were found in an α-santalol ozonolysis caused Simonsen to postulate tautomeric forms for the compound. The equilibrium would be as shown below with the form A being much the more predominant.

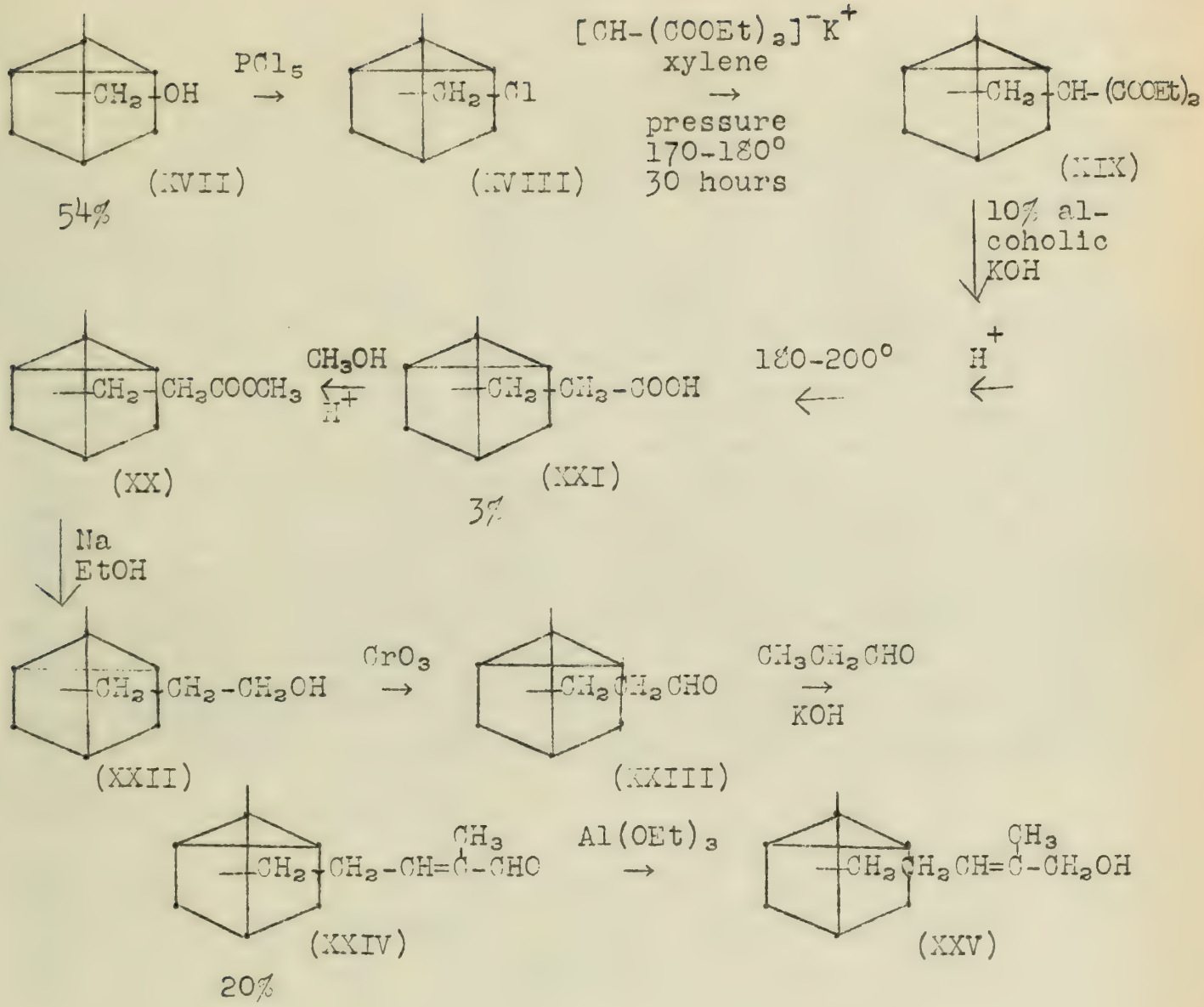


Synthesis of α-Santalol.--Guha and Bhattacharyya have found it possible to synthesize α-santalol using d-α-camphor as a starting material. Their final product was found to be identical with the natural product as shown by the following table of physical constants for the natural and synthetic products. In addition the elementary analyses were found to check well.

Constant	Natural	Synthetic
Unsaturation Number	1.00	1.00
$[\alpha]_{5780}$	+9.02°	+9.60°
$n^{25}D$	1.5016	1.5013
d^{25}_{25}	0.997	0.997

The scheme of synthesis, with yields by individual steps where available, is represented as follows:





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Reported by R. R. Phillips
January 9, 1948

TELOMERS

General.--Recently a new type of polymer, called a telomer, has been discovered. This group of compounds is produced by a process called telomerization (from Greek telas, meaning end and mer meaning part) defined as the process of treating under polymerization conditions, a compound YZ, which is called a telogen, with more than one unit of a polymerizable compound having ethylenic unsaturation. Telomers have the formula $Y\text{-}(A)_n\text{-}Z$ in which $(A)_n$ is a divalent radical formed by the chemical union (with the formation of new carbon to carbon bonds) of monomer molecules, n being any integer greater than one, and Y and Z being fragments of the telogen attached to the terminal groups. It is important to notice that a telomer differs from the usual structural type of polymer in that its components are not present in recurring units; the olefin part is present many times as compared to the adduct and the adduct is always at the end (e.g., $CH_2{=}CH_2 + XY \rightarrow X(CH_2CH_2)_nY$ instead of $-XCH_2CH_2YCH_2CH_2X-$..... or some similar structure). These reactions appear to proceed via a free radical mechanism, and are initiated and catalyzed by compounds which decompose to give free radicals (e.g., peroxides) or by light, which causes liberation of energy with the resultant formation of free radicals.

Examples of telomer formation and industrial applications of these products.--

1. Telomers of structure $H(C_2H_4)_n\text{-}C(R)(OR')(OR'')$ are prepared from ethylene and an acetal (5).

$$CH_3O(CH_3O)CH_2 + 57\ (CH_2{=}CH_2) \xrightarrow[\substack{80^\circ \\ 800\ \text{atm.}}]{Bz_2O_2} H(C_2H_4)_{57}\text{-}C(H)(OCH_3)(OCH_3)$$

The telomeric products are waxy in nature, have good solubility characteristics, and are compatible with paraffin and waxes; in general, they have a high wax-solvent retention, are extremely hard, and form continuous films without stringing or sticking. They can be modified with, for example, a vinyl compound to give tough waxes (e.g., ethylene plus one-hundred parts of vinyl acetate and two-hundred parts of 1,3-dioxolane gives a telomer with ratio of reactants 115:3.1:1 respectively). The fact that no interpolymerization had occurred was proved for this particular group of compounds by boiling with fuming HBr for sixteen hours with no resulting change in molecular weight.

2. Thio-ethers are prepared from ethylene and sulfhydryl compounds, especially H_2S (2). An empirical mechanism is:

$$CH_2{=}CH_2 + H_2S \rightarrow C_2H_5SH$$

$$C_2H_5SH + {}_n(CH_2{=}CH_2) \rightarrow H(CH_2CH_2)_nSC_2H_5$$

3. Fairly high molecular weight waxes are obtained by the polymerization of ethylene in the presence of various oxygen-containing compounds (8). Apparently the presence of a replacable hydrogen atom in the oxygen-containing compound is at least a necessary condition for the occurrence of telomerization. The structure $H(CH_2CH_2)_nR$ may be visualized as resulting from the removal of hydrogen from the telogen, the R representing the telogen residue. Examples of telogens are diethyl malonate and ethyl acetoacetate.

4. Plastic and rubber-like products result from 1,3-dienes and polyhalo alkanes (7). Typical dienes are butadiene, 2-chlorobutadiene, 2-cyanobutadiene, 2,3-dimethylbutadiene. Typical haloalkanes are carbon tetrachloride, bromoform, 1,1,1-trichloroethane and chloroiodomethane. From the low molecular weight polymers obtainable by telomerization, useful products can be synthesized.

5. Polysulfonic acids can be formed from telomers containing aromatic nuclei (4). An aromatic taxogen (e.g., styrene, vinyl benzoate, etc.) treated with a telogen such as carbon tetrachloride forms telomers which, upon sulfonation, yield products most useful when the ratio of sulfonic acid groups to aromatic nuclei is one to one. They are used as bleaching agents for leather and as intermediates in the formation of dispersing agents, surface-active agents, dyes and pigments.

6. Poly-aromatic nitro compounds are obtained by the nitration of telomers formed from styrene in reaction with various telogens (e.g., CCl_4) (6) where n has an average value of twenty-one.

$$n(C_6H_5CH{=}CH_2) + CCl_4 \xrightarrow[86^\circ\ 70\ \text{hrs.}]{Bz_2O_2} Cl(C_6H_5CHCH_2)_nCCl_3$$

Twenty parts of telomer plus one-hundred fifty parts of fuming nitric acid gives a yellow product containing one nitro group per styrene unit; these compounds can be reduced with palladium charcoal to the corresponding amines. They are used as intermediates in the preparation of dispersing agents, surface active agents, dyes and pigments.

<u>Mechanism</u>.--As previously stated, telomerization apparently proceeds via a free radical mechanism. As an example, consider the addition of methyl di-chloro-acetate to an aliphatic olefin.

$$R\text{-}CH{=}CH_2 + CHCl_2COOCH_3 \xrightarrow{\text{peroxide}} RCH_2CH_2CCl_2COOCH_3 +$$

$$RCH_2CH_2RCHCH_2CCl_2COOCH_3 + \text{higher - boilers (telomers)}$$

Using diacetyl peroxide as the catalyst, the products obtained may be accounted for thusly:

$$(CH_3COO)_2 \rightarrow CH_3\cdot + CO_2 + CH_3COO\cdot \quad (A)$$

$$CHCl_2COOCH_3 + CH_3\cdot \rightarrow CH_4 + \cdot CCl_2COOCH_3 \quad (B)$$

$$RCH{=}CH_2 + \cdot CCl_2COOCH_3 \rightarrow R\dot{C}HCH_2CCl_2COOCH_3 \quad (C)$$

$$RCHCH_2CCl_2COOCH_3 + CHCl_2COOCH_3 \rightarrow RCH_2CH_2CCl_2COOCH_3 + \cdot CCl_2COOCH_3 \quad (D)$$

However, instead of step (D), the free radical formed in step (C) could react with another mole of olefin:

$$R\dot{C}HCH_2CCl_2COOCH_3 + RCH{=}CH_2 \rightarrow R\dot{C}HCH_2RCHCH_2CCl_2COOCH_3 \quad (E)$$

Now the product of reaction (E) may react again, either as the free radical in equation (D) to form $RCH_2CH_2RCHCH_2CCl_2COOCH_3$ or via equation (E), (n-1) times to form $H(RCH{-}CH_2)_nCCl_2COOCH_3$, a telomer.

According to Kharash (12), carbon tetra-bromide gives a one to one addition product with ethylene, but carbon tetrachloride, under identical conditions, yields a polymeric material (telomer). This can be explained by consideration of the tendency of various carbon-X linkages, where X is hydrogen or a halogen, for reaction with free radicals.

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Reported by Donald J. Shields
January 9, 1948

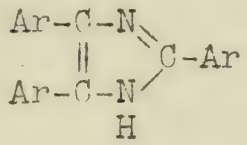
CHEMILUMINESCENCE OF ORGANIC COMPOUNDS

Introduction.--Chemiluminescence refers to the production of light by atoms or molecules which have reached an excited state during the course of a chemical reaction. In order for light of a given wave length to be emitted, it is necessary that the excited atom or molecule possess a certain amount of energy, so in order for a reaction to luminesce it must be exothermic to at least this amount of energy. The phenomenon is observed frequently in reactions of both inorganic and organic compounds. Many reactions result in the emission of ultraviolet light (1), although the reactions giving off visible light have received the most attention. Chemiluminescent reactions of organic compounds in solution appear to be limited to reactions involving oxidation.

The classes of compounds to which most attention has been directed are: (1) Grignard Reagents, (2) Substituted Glyoxalines, (3) Dialkyldiacridinum Salts, (4) Phthalic cyclohydrazides.

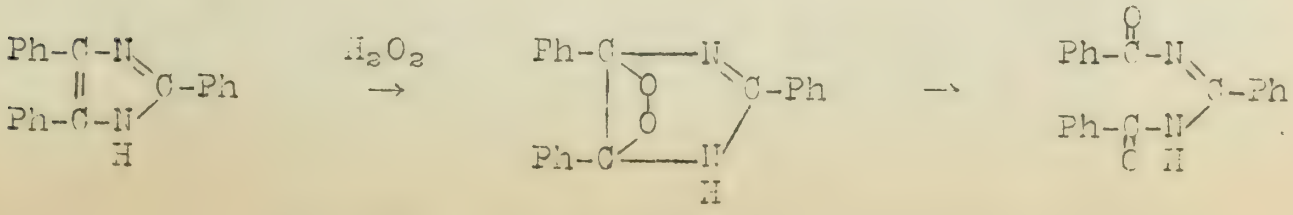
Grignard Reagents.--Aromatic Grignard reagents are more strongly luminescent than the corresponding alkyl compounds when they come in contact with atmospheric oxygen. The nature of the organic part of the reagent has a great influence on the color of light produced. Substitution in the para position enhances the luminescence. The most strongly luminescent Grignard reagent is p-chlorophenylmagnesium bromide. The luminescent reaction probably involves the interposition of an oxygen atom between the aryl group and the metallic atom.

The Triaryl Glyoxalines (I).--The best known of these chemiluminescent substances if triphenyl glyoxaline (lophine) which is prepared by the interaction of benzil, benzaldehyde and ammonia (2,3). These compounds give off light when treated with mild oxidizing agents. The eventual products of the reaction are benzoic acid, ammonia and benzamide.

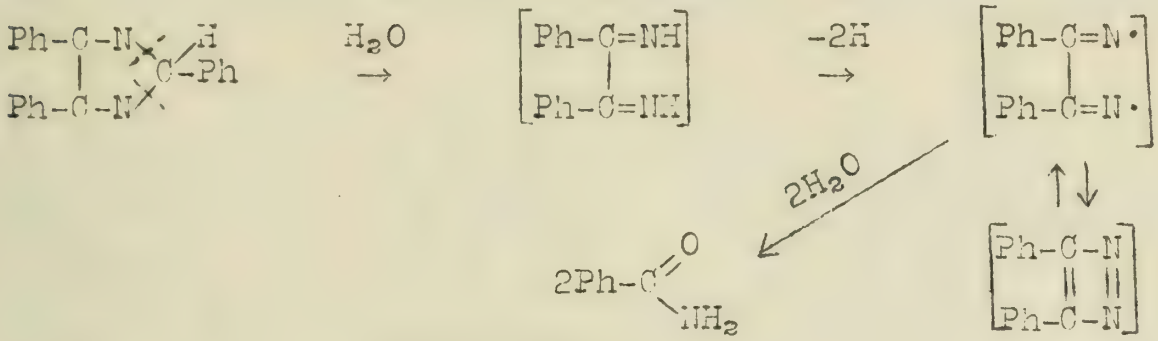


I

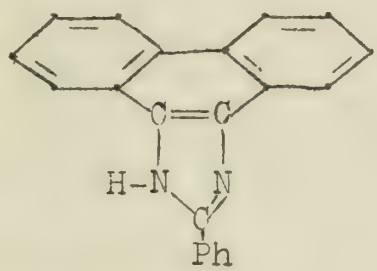
Hatt (4) suggests that the mechanism of the reaction is the formation of a peroxide bridge as an essential step followed by cleavage to give a product which can be hydrolyzed to benzoic acid.



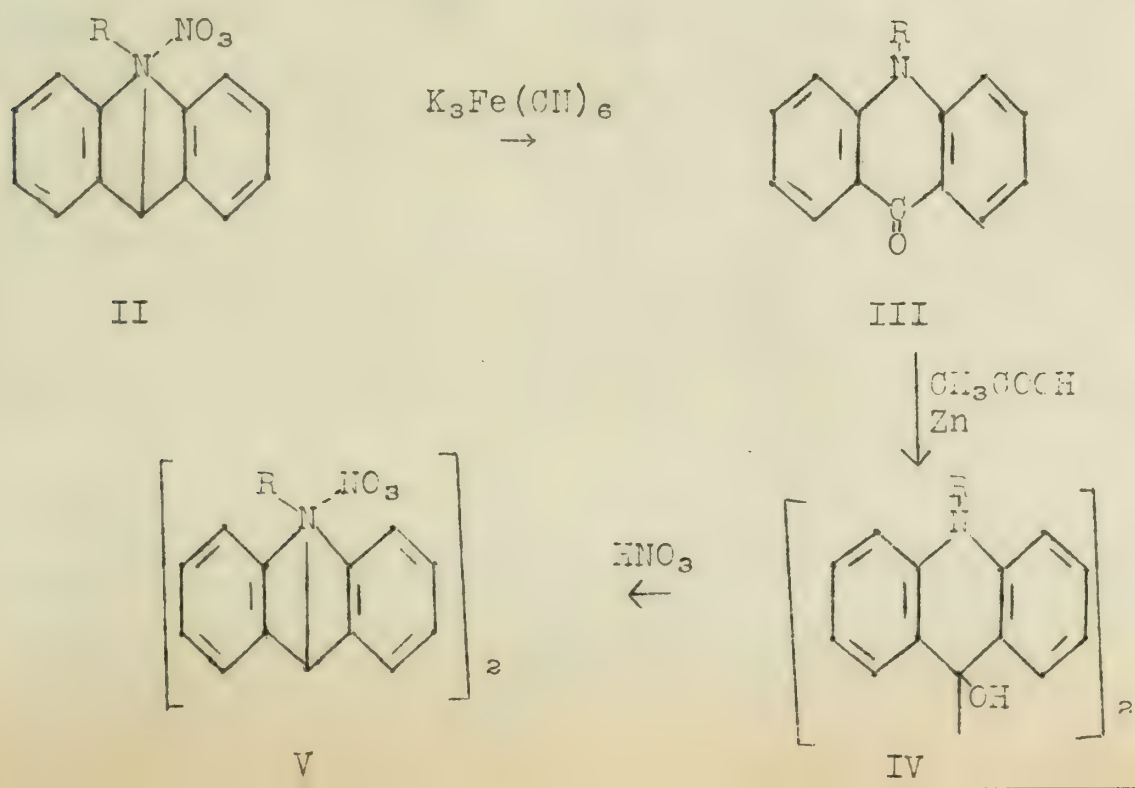
Weiss (6) proposes that hydrolytic cleavage occurs initially, resulting in a compound that should form a radical of the semi-quinone type.



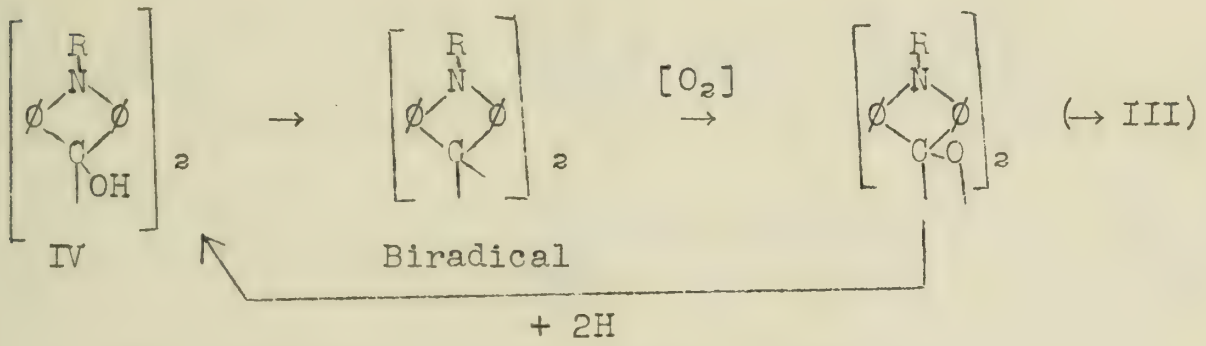
It is interesting to note that the biphenyene derivative is not chemiluminescent (3).



<u>The Dialkyldiacridinium Salts</u>.--(Luzigenin: R = CH_3)
Preparation: (6,7).

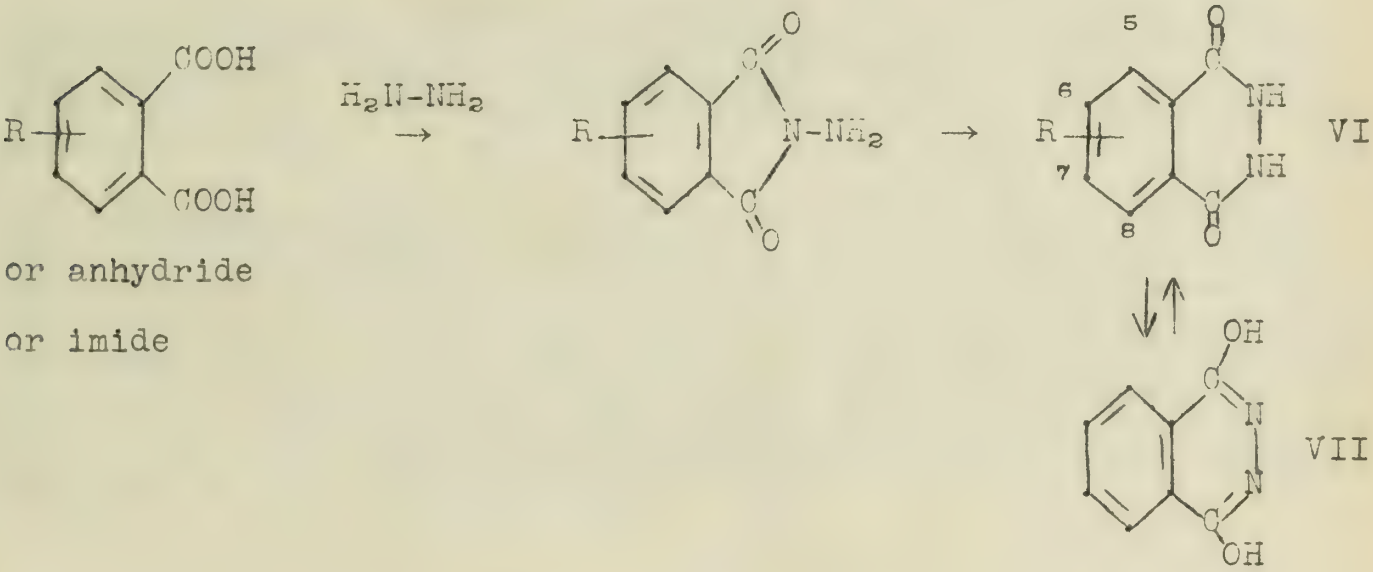


These salts luminesce when treated in alkaline solution with hydrogen peroxide. The reaction is catalyzed by osmium tetroxide. Other oxidizing agents are largely ineffective in producting luminescence. Tamamushi believed that a peroxide is formed from the carbinol base (IV) which would be formed in alkaline solution (8).



The last step in the cycle is said to be responsible for the luminescence. That the luminescent reaction is actually one of reduction is shown by the electrolysis of an alkaline solution of luzigenin (IV), the luminescence appearing at the cathode rather than the anode (8). Moreover, reducing agents, e.g., sulfides or stannites, will cause a brief luminescence if added to an alkaline solution of luzigenin already containing dissolved oxygen.

The Phthalic Cyclohydrazides.--Synthesis: (9) (Luminol: R = 5-amino).

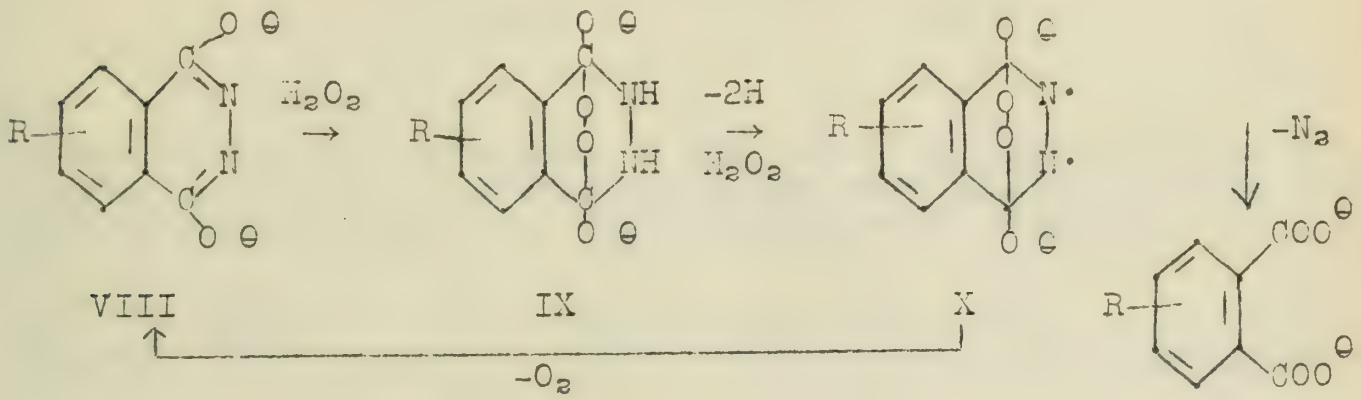


or anhydride

or imide

The necessary structure for chemiluminescence in these compounds seems to be the unsubstituted cyclohydrazide ring. Every compound synthesized thus far which contains such a ring fused to a benzene ring has also exhibited chemiluminescence. Several tautomeric forms are possible for compounds of this type, one of which is shown here.(VII).

Drew (10) claims that form VII would be favored in alkaline solutions and hence is probably the starting point for the luminescent reaction.

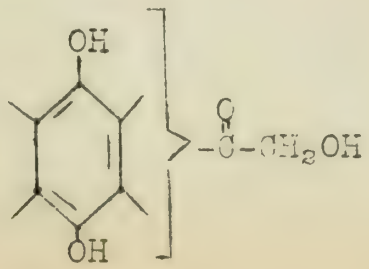


The dilactimic ion is apparently necessary since substitution of one or both of the hydrogens, either on N or O, resulted in products devoid of luminescence.

The influence of substituent groups on the benzene ring of the phthalic derivatives has been studied rather extensively (9). In general it may be said that o-p-directing groups, $-NH_2$, -NHMe, -OH, $-NH-NH_2$ and -Cl, cause an increase in luminescence over that of the unsubstituted parent compound. The meta directing groups have an opposite or, at least, a weaker effect. Substitution of favorable groups in the 5 and 8 positions is more effective in producing luminescence than in the 6 and 7 positions.

Considerable work has been done on the catalysis of the luminol reaction. It was discovered early that hemoglobin acts as a catalyst. Later it was shown that hemin as well as many other naturally occurring metal complexes served to catalyze the reaction (11-13).

Bioluminescence.--The luminescence in fireflies, glowworms and other species is thought to be due to the interaction of a complex organic substance, luciferin, and an enzyme, luciferase, in the presence of oxygen. Little is known of the chemical nature of these substances due to their complexity and the difficulty of isolating appreciable quantities of them in pure form. Chakravorty and Ballentine (14) have shown that highly purified luciferin contains only C, H, and O and probably contains a carbonyl group. They have proposed the partial structure:



They believe that the light producing reaction is involved in the change:

$$R\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}CH_2OH \xrightarrow[O_2]{\text{luciferase}} R\text{-}COOH$$

These workers have been able to regenerate the light-producing luciferin from the luciferin which has been oxidized in the presence of luciferase by the following series of reactions:

$$R\text{-}COOH \xrightarrow{SOCl_2} R\text{-}C\begin{matrix} \diagup O \\ \diagdown Cl \end{matrix} \xrightarrow{CH_2N_2} R\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}CHN_2 \xrightarrow{H_2SO_4} R\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}CH_2OH$$

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Reported by W. V. Ruyle
January 9, 1948

REPLACEMENT OF THE DIAZONIUM GROUP BY THE NITRO GROUP

Introduction.--The replacement of the diazonium group by the nitro group finds limited, but convenient, application in the preparation of aromatic nitro compounds which are not easily synthesized by direct nitration because of adverse directing influences. A few examples of such compounds are o- and p-dinitrobenzene, beta-nitronaphthalene and several of the dinitronaphthalenes.

Historical.--The reaction was first conducted by Sandmeyer (1) in 1887 on aniline to obtain a 42% yield of nitrobenzene. The aniline was diazotized in nitric or sulfuric acid with twice the required amount of sodium nitrite, and the solution was poured into a water suspension of excess cuprous oxide. Sandmeyer by an analogous procedure using beta-naphthylamine obtained beta-nitronaphthalene in 5% yield.

Meisenheimer and Witte (2), by altering Sandmeyer's procedure slightly, obtained a 25% yield of beta-nitronaphthalene, and by the same procedure Meisenheimer and Patzig (3) were able to make p-dinitrobenzene from p-nitroaniline in 23% yield.

Hantzsch and Blagden (4) obtained nitrobenzene by decomposing the double salt of mercuric nitrite and benzene diazonium nitrate with copper powder in almost quantitative yield based on the amount of double salt used. In the preparation of beta-nitronaphthalene they added a solution of the diazonium sulfate to a mixture of cuprous-cupric sulfite and potassium nitrite and obtained a 25% yield from the diazonium salt. Recently, Hodgson, Mahadevan, and Ward (5) have reinvestigated the cuprous-cupric sulfite method but used sodium nitrite in place of potassium nitrite and a somewhat differently prepared copper solution. Yields on amines investigated ranged from 15 to 65%.

A further modification was made by Vesely and Dvorák (6) who added the diazotized amine to an excess of Gattermann's molecular copper (copper bronze can be used) and aqueous sodium nitrite and obtained yields from zero to 61%.

Bucherer and von der Recke (7) simply added the diazonium solution to varying excesses of sodium nitrite and hydrochloric acid to ascertain optimum conditions. They found the yield of nitro compound to increase with increase in the concentration of sodium nitrite and to vary from 4 to 58% with the amines investigated.

In 1937 Starkey (8) employed the diazonium boroflourides (obtained by a method (9) superior to Balz and Schiemann's (10) earlier procedure for the boroflourides) for the nitro group replacement in the following manner: the diazonium salt as a thin aqueous paste was added portionwise to a well stirred mixture of copper powder in a water solution of sodium nitrite. He lists yields for the amines studied from less than 10% to as high as 64%.

A Recent Method.--It has been found that good yields of the nitro compound can be obtained from the decomposition of diazonium cobaltinitrite complexes. Hodgson and Marsden (11) have prepared these complexes for several amines and the list has been extended by Hodgson and Ward (12).

The complexes are obtained in almost quantitative yield by adding a cold, filtered diazonium solution of the amine with stirring to a mixture of chalk and ice. The resulting solution is then filtered with suction into an aqueous solution of sodium cobaltinitrite contained in the filter flask; after fifteen minutes the complex is separated by filtration, washed with water, followed by ether. The complexes are bright yellow to orange in color, and those from the nitro- and chloroanilines are stable when dry, but those from the toluidines, anisidines, and alpha-naphthylamine are less stable. On heating, the complexes decompose, often with explosive violence. They couple with alkaline beta-naphthol, with alpha- and beta-naphthylamine in acetic acid solution, but in hydrochloric acid they diazotize amines and nitrosate phenols by the nitrous acid liberated.

Three procedures, differing only in temperature and duration of decomposition, are available for the replacement reaction. The first or "hot" decomposition is effected by gradually adding an aqueous slurry of the cobaltinitrite complex to a vigorously stirred mixture of sodium nitrite, copper sulfate, and cuprous oxide in water at 60° to 70°; decomposition is complete in about fifteen minutes. The second or "cold" procedure is carried out by stirring the reaction mixture in the cold for twenty-four hours. In the third procedure the reaction is conducted at room temperature until evolution of nitrogen has ceased.

The cold procedure is recommended for those end compounds which have melting points below 120°. The yield of nitro compound ranges from 68% to traces for those complexes thus far investigated. A 60% yield in the case of beta-nitronaphthalene is claimed.

In the accompanying table the per cent yields of nitro compounds obtained by replacement of the diazonium group by various procedures are listed. The nitro compounds indicated by # appear to be best prepared by the replacement reaction; there are very probably several other nitro compounds best prepared by this means that have not been listed.

% YIELDS OF NITRO COMPOUND BY REPLACEMENT OF DIAZONIUM GROUP BY DIFFERENT PROCEDURES BASED ON AMINE USED

Amine Used	Nitro Compound	cobaltinitrite procedures 3rd	1st	2nd	Starkey	Hantzsch and Blagden	Hodgson, Mahadevan and Ward	Veseley and Dvorak	Bucherer and von der Recke
o-nitroaniline	# o-dinitrobenzene	67			33				37-58
p-nitroaniline	# p-dinitrobenzene	56			64				42-58
m-nitroaniline	m-dinitrobenzene	65			43				18-30
p-chloroaniline	p-chloronitrobenzene	69				65*			22
α-naphthylamine	α-nitronaphthalene	56			<10	25*			4
β-naphthylamine	# β-nitronaphthalene	60	45				40	28.2	5.5 -3-
p-toluidine	p-nitrotoluene	69*			10				
p-aminoanisole	p-nitroanisole	68*							
o-toluidine	o-nitrotoluene	61							
o-aminoanisole	o-nitroanisole	63							
2-nitro-1-naphthylamine	# 1,2-dinitronaphthalene		5	5			53*		
1-nitro-2-naphthylamine	1,2-dinitronpahthalene		Tr	Tr			15*	zero	
4-nitro-1-naphthylamine	# 1,4-dinitronaphthalene		15	30			65	poor	
5-nitro-1-naphthylamine	1,5-dinitronaphthalene		30						
5-nitro-2-naphthylamine	# 1,6-dinitronaphthalene			40			55	22	
6-nitro-2-naphthylamine	2,6-dinitronaphthalene		40	50			45		
8-nitro-2-naphthylamine	# 1,7-dinitronaphthalene		45	40			45	22	
benzidine	4,4'-dinitrobiphenyl		20	40			16		
3,3'-dinitrobenzidine	3,3',4,4'-tetranitrobiphenyl						55		
3,5-dinitro-p-toluidine	# 3,4,5-trinitrotoluene						25		
2,4,6-tribromoaniline	# 2,4,6-tribromonitrobenzene					65*			

3rd - reaction at room temperature
1st - reaction at 60 to 70 degrees
2nd - reaction in the cold for 24 hours
* yields based on diazonium salt used

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Reported by Clifford D. Marshall
January 9, 1948

RECENT APPLICATIONS OF POLAROGRAPHY IN ORGANIC CHEMISTRY

General Principles.--The polarographic method of chemical analysis is based on the interpretation of the current-voltage curves that are obtained when solutions of electroreducible or electroöxidizable substances are electrolyzed in a cell in which one electrode consists of mercury falling dropwise from a very fine bore capillary glass tube. From the unique characteristics of such current-voltage curves both the species and concentration of the substances present in the solution can be determined. A few terms must be defined. Residual current is the small current which flows for a solution containing no substances which are reducible at the electrode. Continuous electrolysis begins at the decomposition potential. At the half-wave potential the current is one-half of its limiting value, the diffusion current. When the limiting current is flowing, the electrode is said to be concentration polarized. The concentration of the reducible material is depleted close to the surface of the electrode, and the current is proportional to the concentration of the material in solution. For a complete discussion of the theory, apparatus and technique of polarography see the texts by Kolthoff and Lingane (1) and Kolthoff and Laitinen (2).

Organic Polarography.--Developments in the field of organic polarography to 1940 have been summarized in previous seminar reports (3,4,5).

Dialkyl ketones are not reduced, but aromatic ketones and aliphatic-aromatic ketones are readily reduced. Aliphatic aldehydes are reduced. One of the easiest reductions is that of quinone to hydroquinone. Sex hormones give a wave only if the double bond is conjugated with a carbonyl group. Saturated acids are not affected. Unsaturated acids and esters give a wave if the double bond is alpha-beta. Aliphatic amines are reduced at very negative potentials, -2.0v., but give no well-defined diffusion currents. Pyridine readily reduces to piperidine. Aromatic nitro compounds reduce to amines, azo compounds to hydrazo compounds. If the reduction of an organic compound is irreversible, the nature of the reduction products is unknown.

Hydrogen Bonding and Chelate Rings.--Astle (6) has found that the half-wave potentials for o-nitro phenols are more positive than those for p-nitrophenols or o-nitroanisole in acid solutions. The value is the same for all three in basic solutions since there can be no hydrogen bonding with the phenolate. The wave height for reduction of o-nitro phenol is two-thirds the value in a base. This indicates the intermediate hydroxylamine is sufficiently stabilized by the presence of a hydrogen bond so that complete reduction to the amine is not possible at the dropping mercury cathode.

$$-NO_2 \xrightarrow{2e^-} -NO \xrightarrow{2e^-} -NOH \xrightarrow{2e^-} -NH_2$$

When the hydroxyl group is ortho to the nitro, it is reduced at more positive potentials than when para or meta (7). If it is para, the nitro group is reduced to the amine at all pH. The meta compounds are reduced only to the hydroxyl amine stage in basic solutions since they cannot form quinoid structures.

Reduction of Unsaturated Hydrocarbons.--Laitinen (8) has studied reduction of phenyl substituted olefins and acetylenes. It was found that the half-wave potential is a good measure of the relative activation of ethylenic linkages by substituent groups. The results are presented in the table.

COMPOUND	HALF-WAVE POTENTIAL
$\emptyset CH{=}CH_2$	-2.34 v.
$\emptyset CH{=}CH\emptyset$	-2.14
$\emptyset_2 C{=}CH_2$	-2.26
$\emptyset_2 C{=}CH\emptyset$	-2.12
$\emptyset_2 C{=}C\emptyset_2$	-2.05

An isolated double bond is not reduced. A similar reaction between activation and potential was found in the acetylene series.

Use of the polarograph to determine mechanisms is illustrated in this experiment. The reduction was performed varying the concentration of material. The half-wave potential was independent of the concentration, hence of the hydroxyl concentration. This eliminated several proposed paths of reaction and suggested that the following was the actual mechanism:

$$R + e^- \rightleftarrows R^-$$

$$R^- + e^- \rightarrow R^=$$

$$R^= + 2\,H_2O \rightarrow RH_2 + 2\,OH^-$$

Similar results were reported by Fernelius using sodium in liquid ammonia.

Experiments have been performed in this laboratory (9) on the reduction of polynuclear atomatic compounds. It was found that these hydrocarbons were reduced only if they have a diminished degree of resonance. Naphthalene is reduced by 1,4-addition and goes no further since only two electrons are required. If the addition were 1,2 the product would still possess conjugation and

could be further reduced. Two applications of this procedure are suggested, quantitative determination of the hydrocarbon, and determination of the arrangement of double bonds in the various rings.

Tautomerism.--Laitinen (10) has investigated the behavior of gamma keto acid derivatives at the dropping mercury electrode. The ester of 2-benzoylbenzoic acid can exist in open and cyclic forms. Both forms are reduced but at different potentials and with different intermediates. This suggests that the polarograph may be used to distinguish between the cyclic and normal esters. The normal ester would have a half-wave potential that varies with pH. Unlike physical methods usually employed, both isomeric forms would not be needed.

Enol-keto tautomerism has been investigated by the use of polarography. There is still argument as to whether the two waves obtained in enol-keto systems represent actual amounts of the forms present. It has been suggested that what is measured is the rate of transformation of one form to the other.

Aliphatic Polyene Aldehydes.--Fields and Blout (11) have studied crotonaldehyde and its vinylogs to determine the effect of increasing the chain length on the ease of reduction and on the nature of the products of the electrode reaction. Each compound showed a well-defined wave in pH 1 to 11. A second wave of the same height as the first was observed for each compound over a more limited range of pH. This would suggest one-electron reduction to a free radical, which undergoes dimerization to produce the unsaturated pinacol. The ease of reduction increases with the number of double bonds conjugated with the carbonyl group. The half-wave potentials shift toward less negative values as the number of double bonds increases. The increment shift per double bond decreases as the chain is lengthened.

Applications of Organic Polarography.--Atkinson (12) has established the potentials at which large scale electrolytic reduction of diazotized amines is to be performed.

It has been reported (13) that saturated unsubstituted ketones which are not reduced can be analyzed polarographically in acid hydrazine solution. Concentrations as low as 0.0001M can be determined with a relative accuracy of five per cent.

Most alkaloids are not reducible (14), but instead give waves from catalytic discharge of hydrogen. Cocaine can be detected in 10^{-7}M solutions.

Tomkins (15) has given a polarographic characterization of nicotinic acid and related compounds. Lingane (16) investigated the behavior of riboflavin, thiamine, nicotinic acid and pantothentic acid. Riboflavin is most easily reduced and can be determined in the presence of the others. Many other biological applications are given in the book by Lingane (1).

Problems in Organic Polarography.--For working with organic compounds there is as yet no good non-aqueous solvent. Ethylene dichloride and liquid ammonia have been used but are not entirely satisfactory. Since the new supporting electrolytes permit use of much lower voltages, many early experiments which indicated negative results should be repeated. Especially needed is a thorough investigation of simple systems including determination of mechanisms and products.

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Reported by C. B. Thompson
January 16, 1948

REACTIONS OF LEAD TETRAACETATE

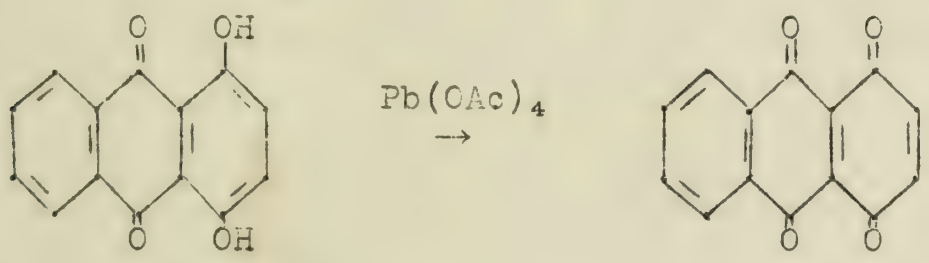
Lead tetraacetate was first isolated by Jacquelin in 1851. It was used in place of PbO_2 as an oxidizing agent in organic chemistry. Since that time the number and variety of reactions for which $Pb(OAc)_4$ can be used has expanded rapidly. It can be prepared in 100% purity and used in calculated amounts. Perhaps the most important property of $Pb(OAc)_4$ is its solubility in organic solvents by virtue of which oxidation may be carried out in a homogeneous solution.

Lead tetraacetate is prepared by the action of acetic acid on Pb_3O_4 (1).

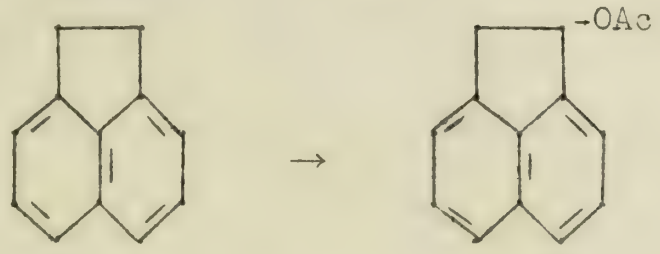
$$Pb_3O_4 + 8\ HOAc \rightarrow Pb(OAc)_4\downarrow + 2\ Pb(OAc)_2 + 4\ H_2O$$

$$2\ Pb(OAc)_2 + Cl_2 \rightarrow Pb(OAc)_4 + PbCl_2$$

I. <u>Dehydrogenation with $Pb(OAc)_4$</u>.--$Pb(OAc)_4$ can convert all hydroquinones to quinones and all leuco dyes to dyes. Difficultly prepared di- and triquinones of the anthraquinone series may be synthesized with this reagent (2).



II. <u>Substitution of -H by $-OCOCH_3$</u>.--Benzene and aliphatic hydrocarbons are inert to the action of $Pb(OAc)_4$. Compounds with active methylene groups are readily attacked.



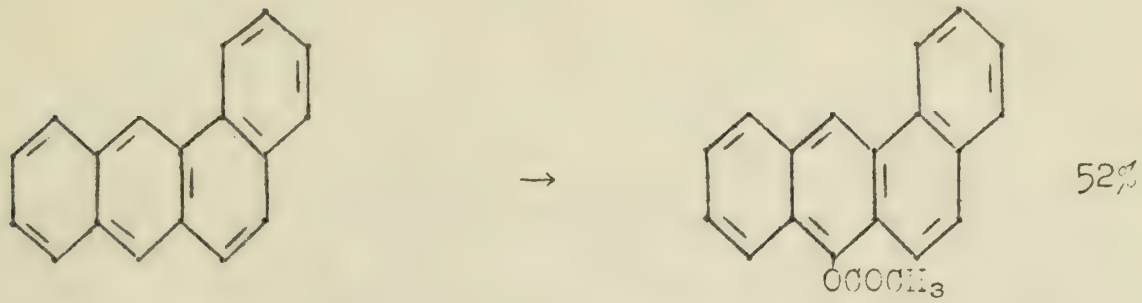
$$\emptyset_3CH \rightarrow \emptyset_3COAc$$

$$\emptyset_2CH_2 \rightarrow \emptyset_2CHOAc$$

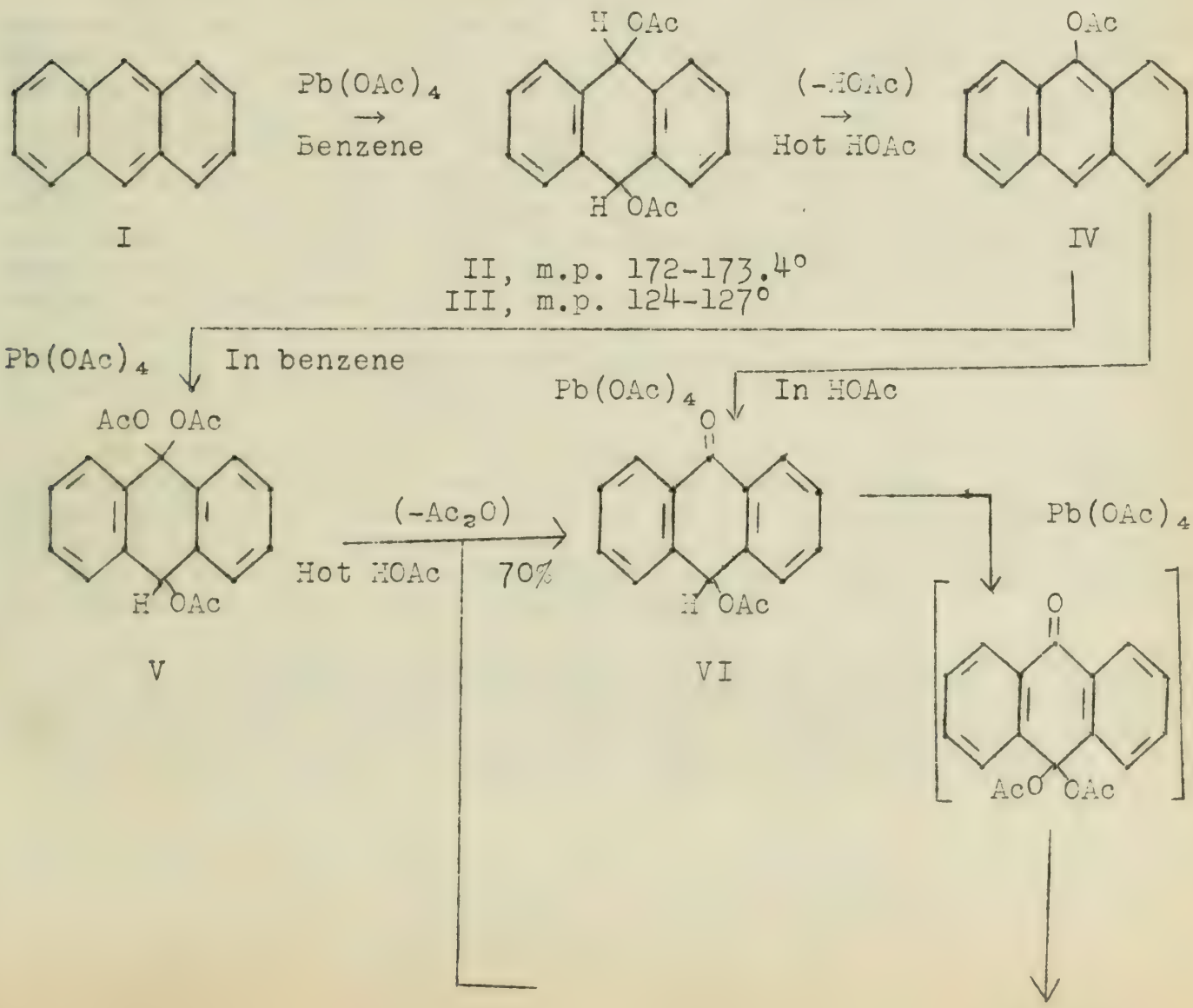
$$\emptyset CH_3 \rightarrow \emptyset CH_2OAc$$

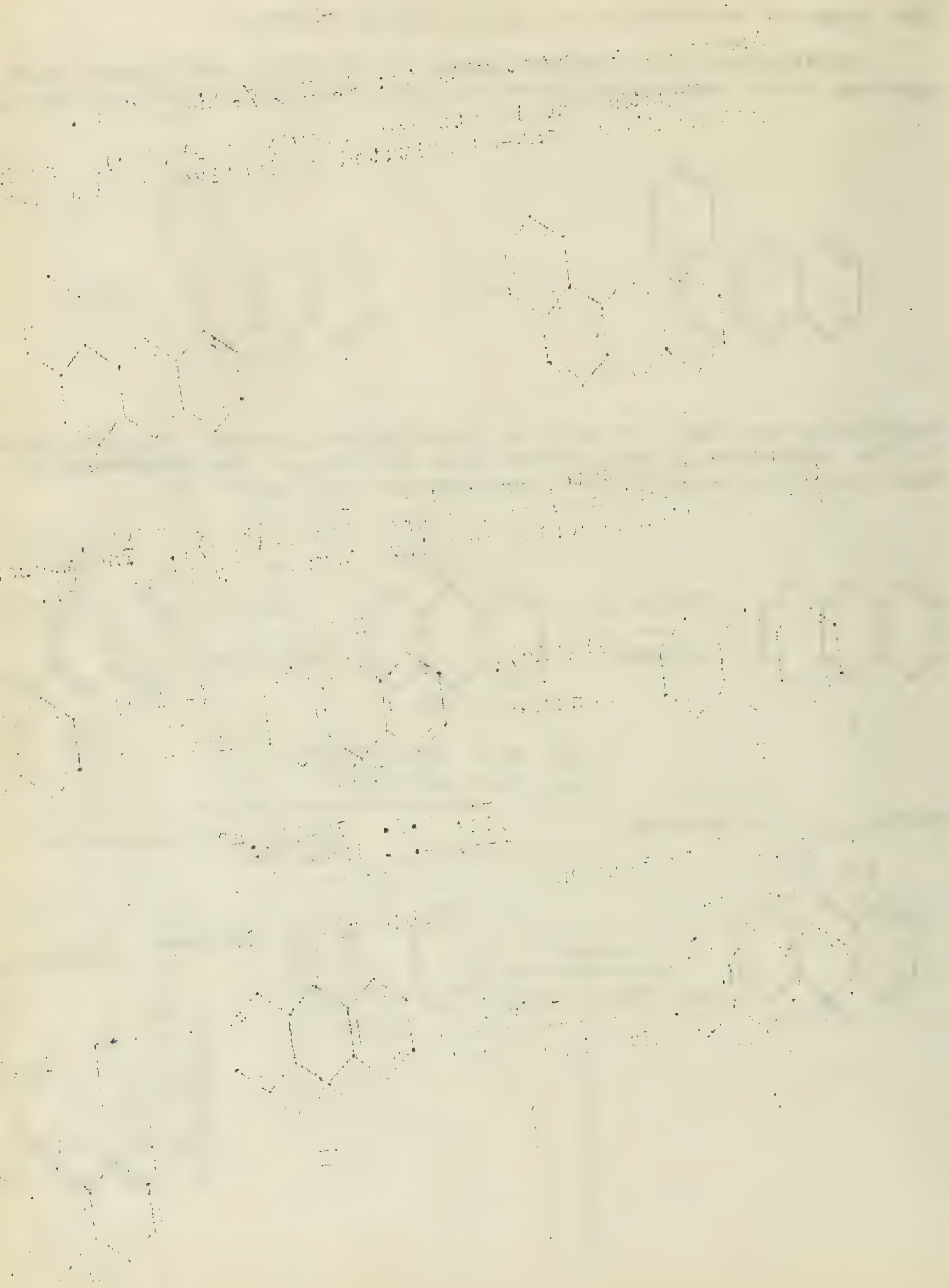
The order of reactivity is: $\emptyset_3CH > \emptyset_2CH_2 > \emptyset CH_3$.

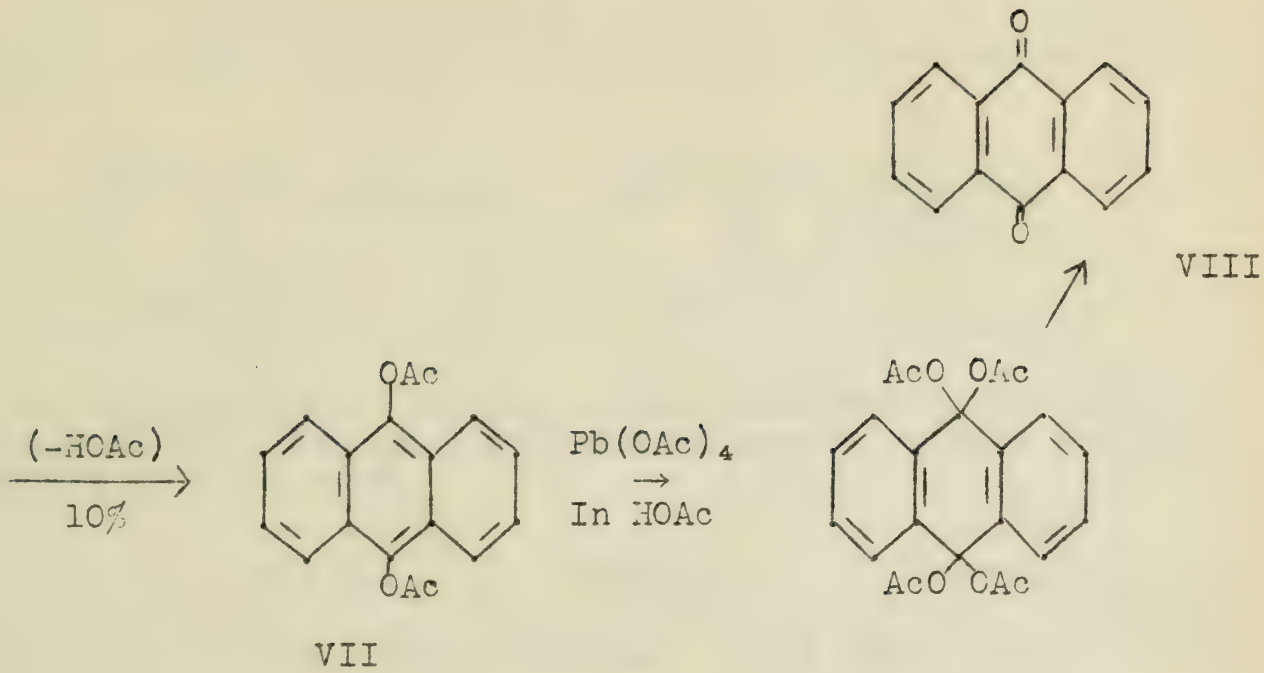
Naphthalene is attacked slowly by $Pb(OAc)_4$ and higher ring systems yield mono-substituted derivatives of the hydrocarbon (3).



Oxanthrone acetate, as well as 9-acetoxyanthracene, was isolated in the oxidation of anthracene with $Pb(OAc)_4$. The mechanism of this reaction recently was investigated by Fieser (4).



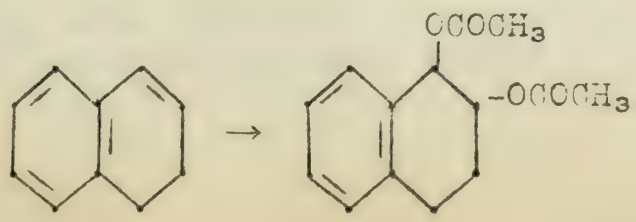




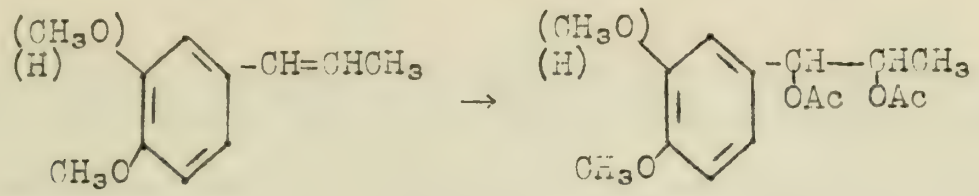
The first step of the reaction is an addition to the aromatic system of two acetoxyl groups. Compounds II and III are considered geometrical isomers since they have the same composition, and by heating either isomer in warm HOAc, 9-acetoxyanthracene is produced. Oxidation of this compound with $Pb(OAc)_4$ in glacial HOAc yields only oxanthrone acetate. No 9,10-diacetoxyanthracene was found, though it could arise from a substitution reaction. If a second addition (similar to the first step) occurred, the initial product should be V, and this compound was isolated when the reaction was carried out in benzene solution. When heated in HOAc, V is converted to oxanthrone acetate VI (70%) by the loss of Ac_2O and 9,10-diacetoxyanthracene by the loss of HOAc. Both oxanthrone acetate and 9,10-diacetoxyanthracene are converted to anthraquinone by $Pb(OAc)_4$ in HOAc solution.

It should be noted that, according to the postulated mechanism, the acetoxyl group in oxanthrone acetate is attached to a different carbon atom than the acetoxyl group in 9-acetoxyanthracene. 2-Methyl-9-acetoxyanthracene was synthesized and oxidized with Pb(OAc) in HOAc solution to the oxanthrone acetate. Its structure was established through an unequivocable synthesis.

III. Addition to Double Bonds.--Although $Pb(OAc)_4$ does not add to aliphatic double bonds, it adds to Δ^1dihydronaphthalene, styrene, and indene to give 50% yields of the trans isomers. Nevertheless, the formation of cis compounds is possible.



With $-OCH_3$ groups present on the ring, the reaction goes more smoothly to give a mixture of the possible steroisomers (5).

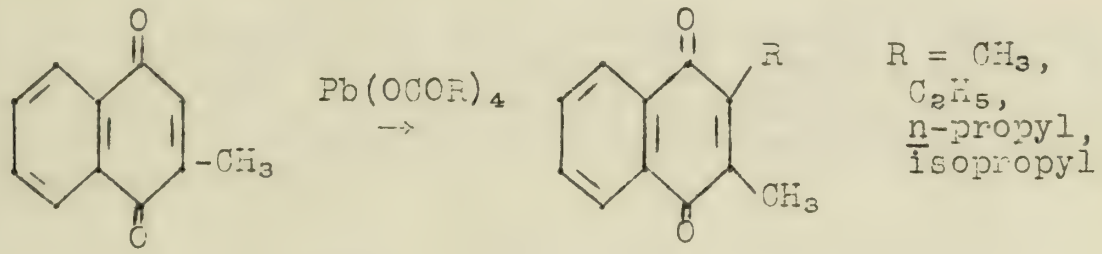


IV. Methylation.--In 1942, Fieser discovered that $Pb(OAc)_4$ was capable of acting as a methylating agent. A free radical mechanism is postulated.

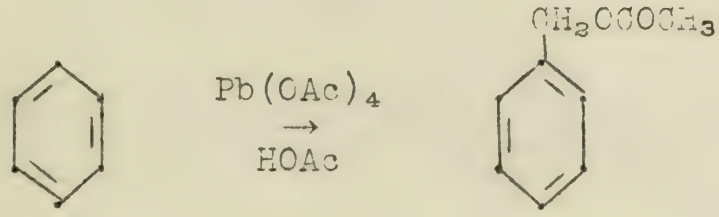
$$Pb(OAc)_4 \rightarrow Pb(OAc)_2 + 2 \cdot OCOCH_3$$

$$2 \cdot OCOCH_3 \rightarrow 2\ CO_2 + 2\ CH_3\cdot$$

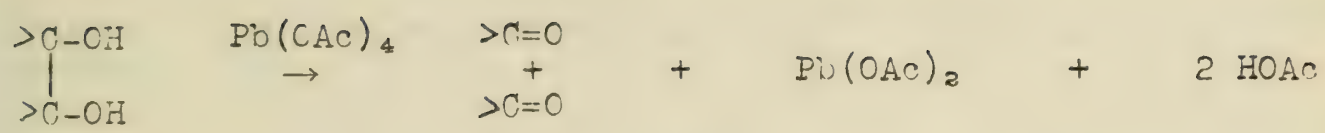
By use of the appropriate tetraesters of lead, the alkylating agent may be methyl, ethyl, n-propyl, or isopropyl (6).



T.N.T. when treated with $Pb(OAc)_4$ yielded trinitro-m-xylene. T.N.B. similarly yielded a mixture of T.N.T. and trinitro-m-xylene. By refluxing benzene with HOAc and $Pb(OAc)_4$, both methylation and replacement of a H by $-OCOCH_3$ take place as the product is benzyl-acetate (7).

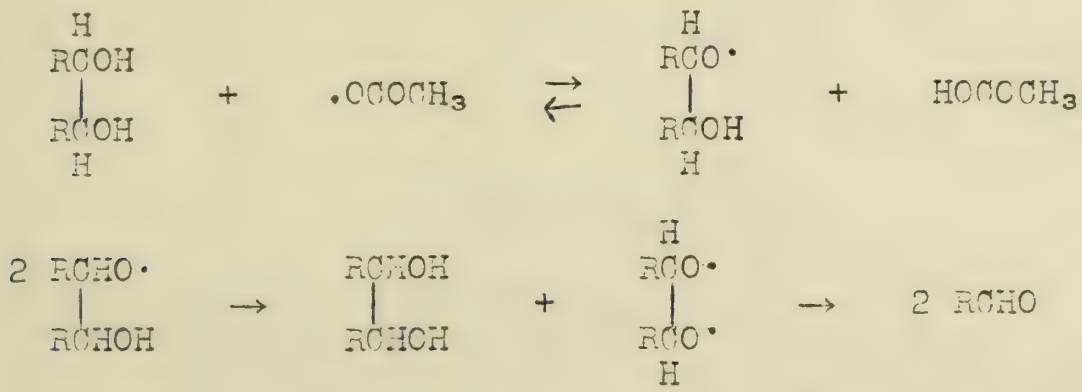


V. Glycol Cleavage.--The oxidation of 1,2-glycols to aldehydes and ketones is perhaps the most important reaction of $Pb(OAc)_4$.

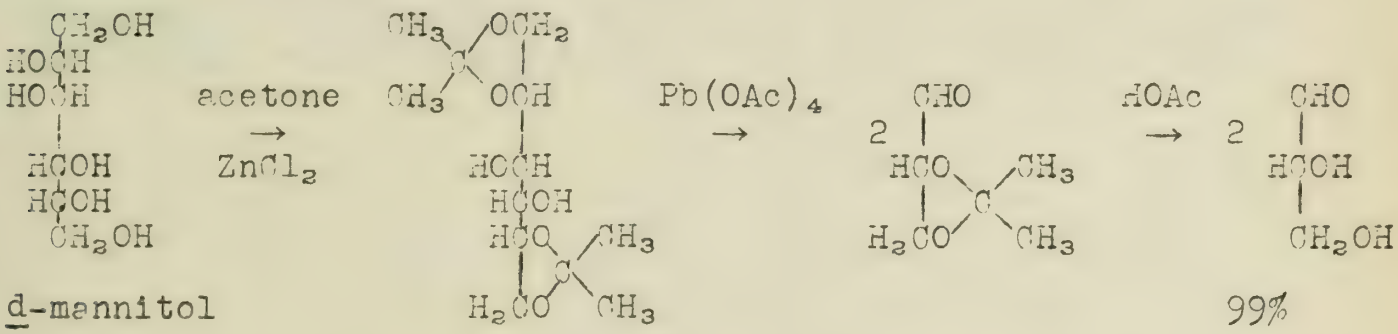


$Pb(OAc)_4$ oxidizes α-hydroxy acids and oxalic acid; HIO_4 will not react with the latter and only very slowly with the former.

A mechanism recently proposed for the glycol cleavage is as follows (8, 9):

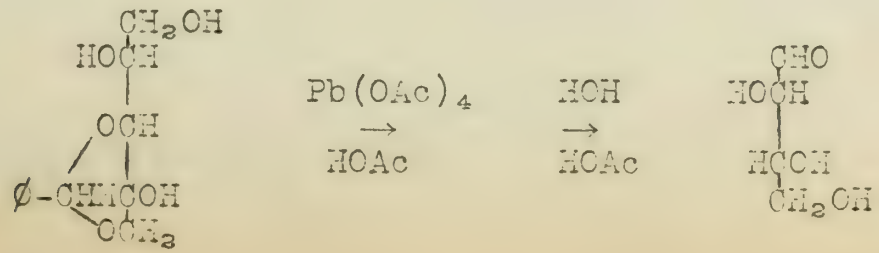


The use of $Pb(OAc)_4$ or HIO_4 for the glycol cleavage has been a matter of preference of the investigator. This cleavage is of great importance in the preparation of certain rare sugars and in the structure proof of others. d-Glyceraldehyde is obtained by the following steps (10):

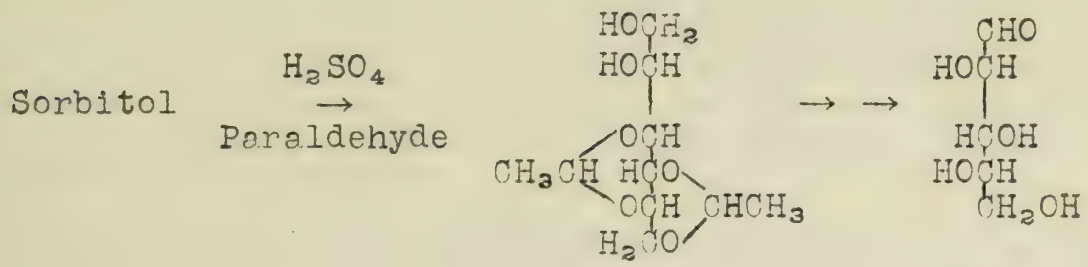


d-mannitol 99%

l-Glyceraldehyde may be formed from l-mannitol in the same manner (11). d-Threose can be obtained from oxidation of benzalarabitol (12).



Similarly l-xylose can be prepared in 90% yields from diethylidine sorbitol (13).



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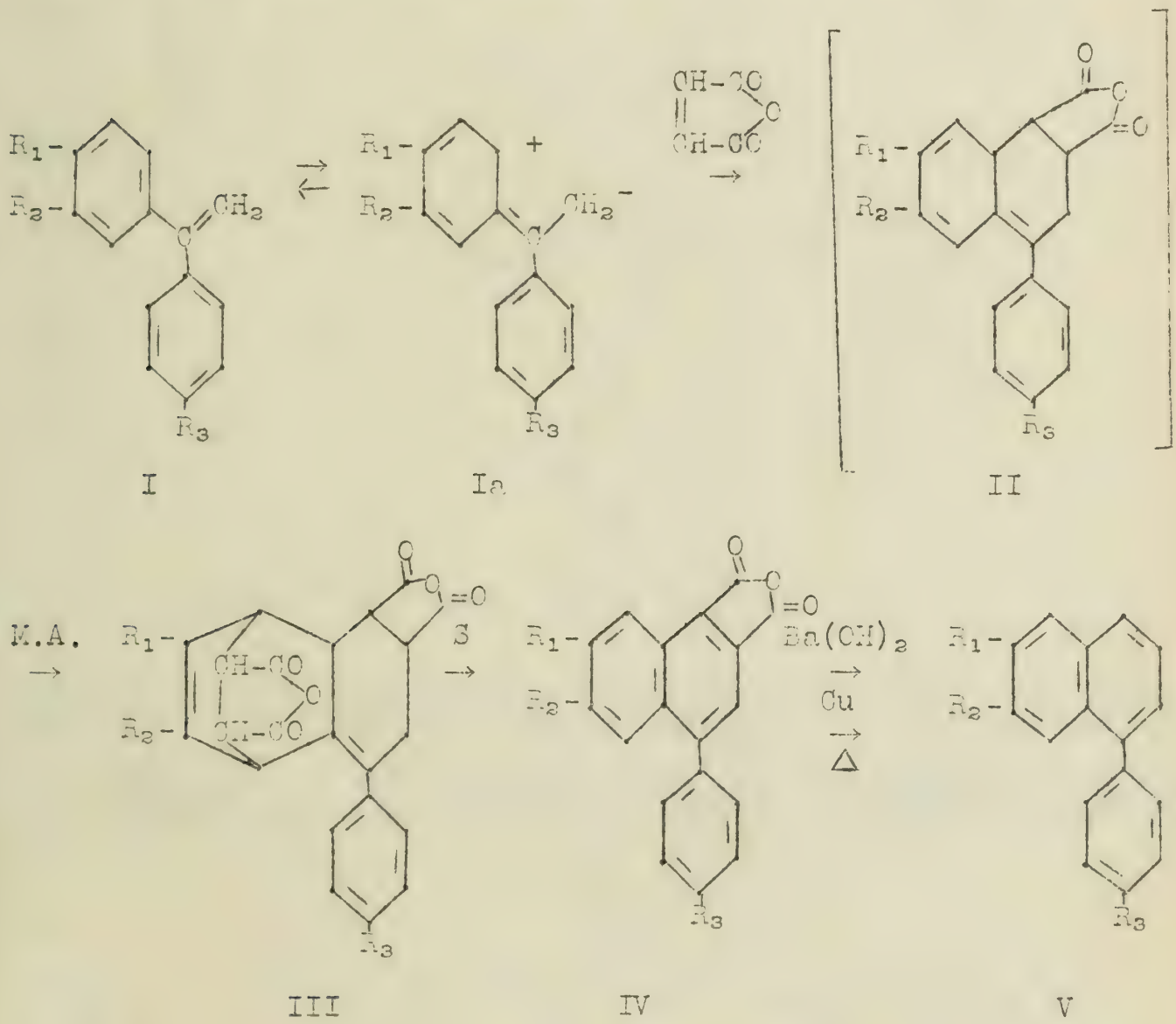
Reported by William C. Wildman
January 16, 1948

THE DIELS-ALDER REACTION INVOLVING A DOUBLE BOND OF AN AROMATIC NUCLEUS

The first incidence of the addition of a dienophile, such as maleic anhydride, to a diene system in which one of the double bonds is furnished by an aromatic nucleus and the other by an exocyclic double bond was observed by Wagner-Jauregg in 1930 (1). 1,1-Diphenylethylene reacted with two molecules of maleic anhydride to form a bis-adduct, but the structure of the adduct was not elucidated at that time.

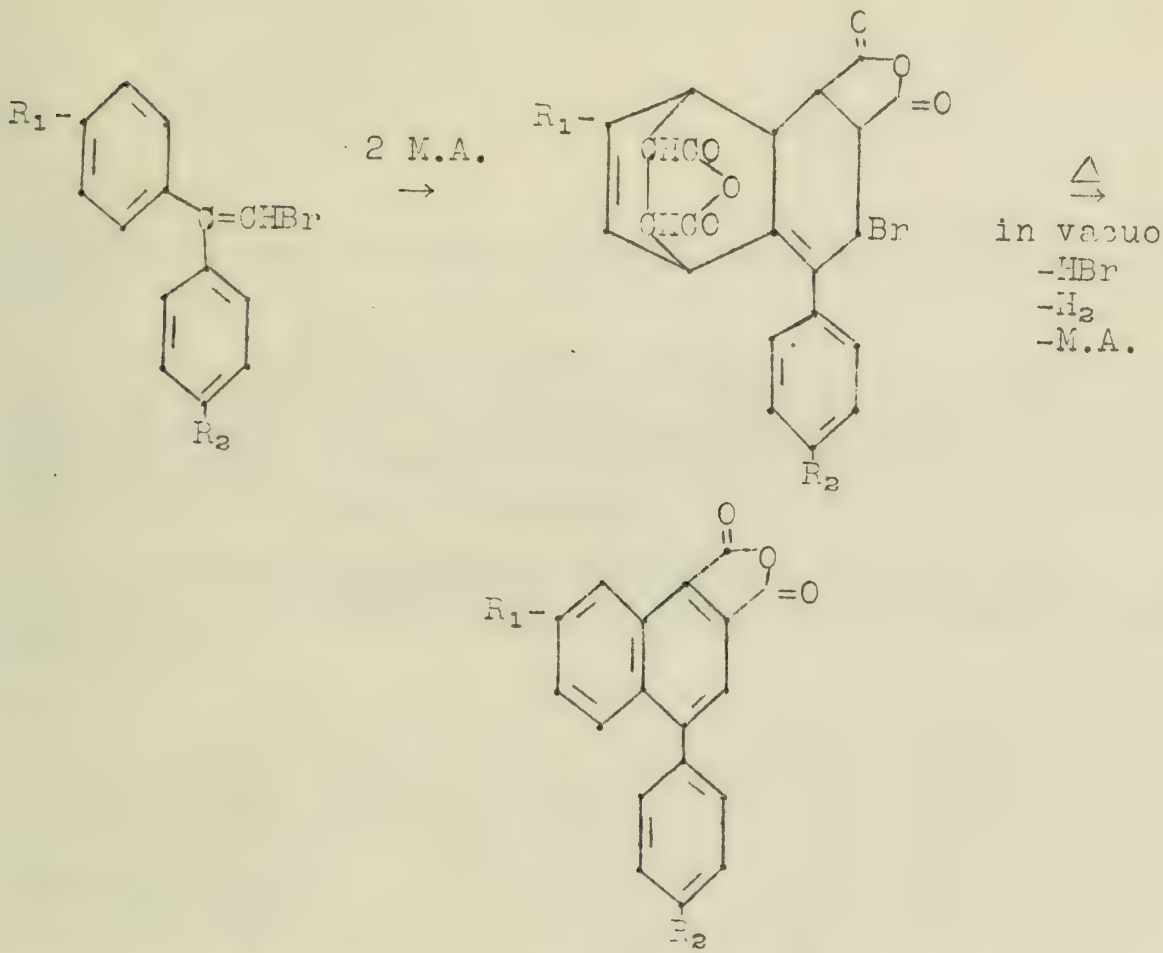
Considerable light was cast on this reaction in 1947 by Bergmann, Szmuszkowicz and Fawaz (2). These authors employed substituted 1,1-diphenylethylenes and propose the following scheme for the progress of the reaction:



(1) $R_1=OCH_3$; $R_2=R_3=H$; (2) $R_1=R_2=R_3=H$; (3) $R_1=OCH_3$; $R_2=H$; $R_3=OCH_3$; (4) $R_1=R_2=OCH_3$; $R_3=H$; (5) $R_1=R_2=R_3=OCH_3$; (6) $R_1=C_6H_5$; $R_2=R_3=H$; (7) $R_1=R_2=H$; $R_3=CH_3$.

Some of the ethylenes were unstable and were replaced by the corresponding ethanols as starting materials. The ethanols reacted in a like manner.

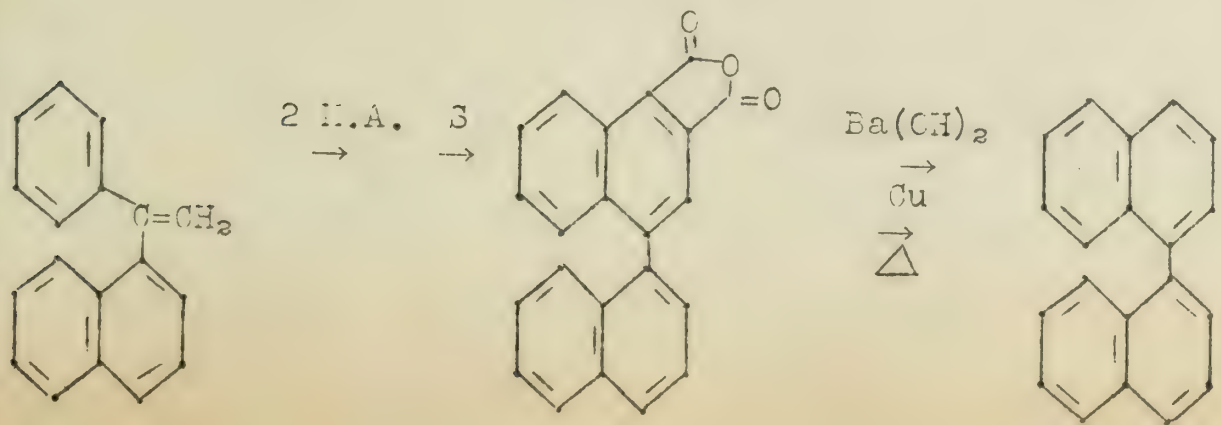
Diarylvinyl bromides can also be used in the Wagner-Jauregg reaction (3).

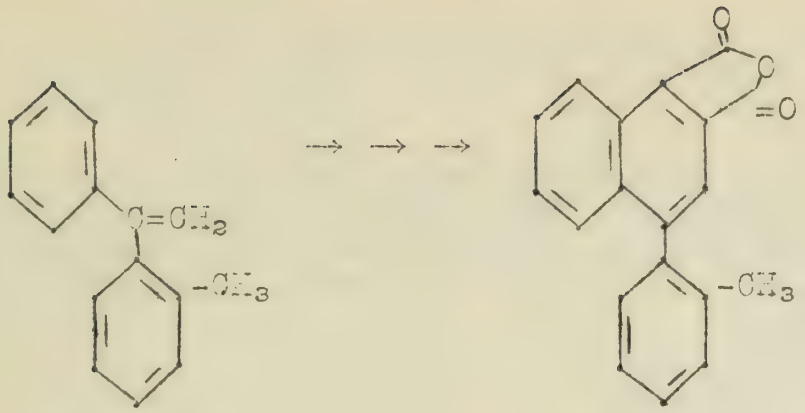


$R_1=R_2=H$; $R_1=R_2=CCH_3$; $R_1=Br$; $R_2=H$; $R_1=C_6H_5$; $R_2=H$.

Neither triphenylethylene nor 1,1-di-(p-chlorophenyl)-2,2-dichloroethylene could be brought into reaction with maleic anhydride.

Szmuszkowicz and Bergmann have shown that ortho substituents in 1,1-diarylethylenes hinder the reaction with maleic anhydride (4).

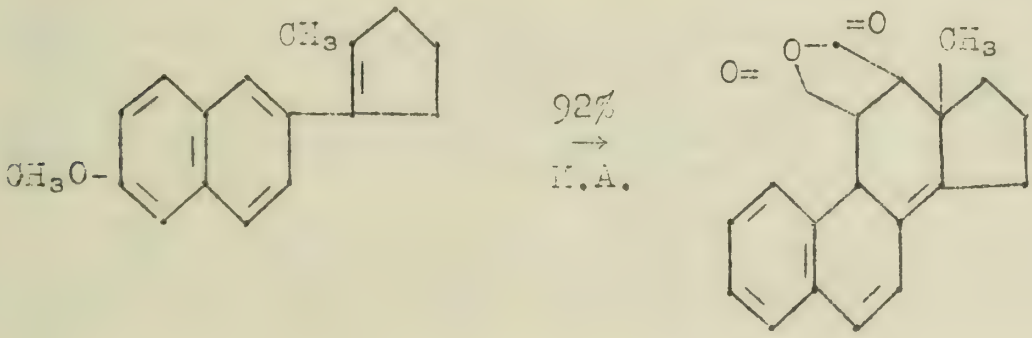




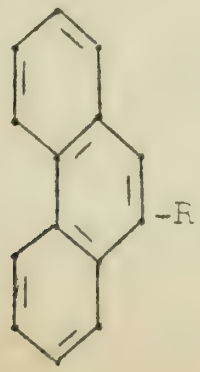
1,1-Di-α-naphthylethylene does not undergo the Wagner-Jauregg reaction at all.

Cohen and Warren treated substituted vinylnaphthalenes with maleic anhydride in a study of compounds related to the sterols and bile acids (5). 1-Vinylnaphthalene, 2-vinylnaphthalene and 6-methoxy-1-vinylnaphthalene react with one molecule of maleic anhydride in the expected manner.

Bachmann and Kloetzel studied the diene synthesis using substituted 1-cyclopentenylnaphthalenes (6). A typical example is shown below.



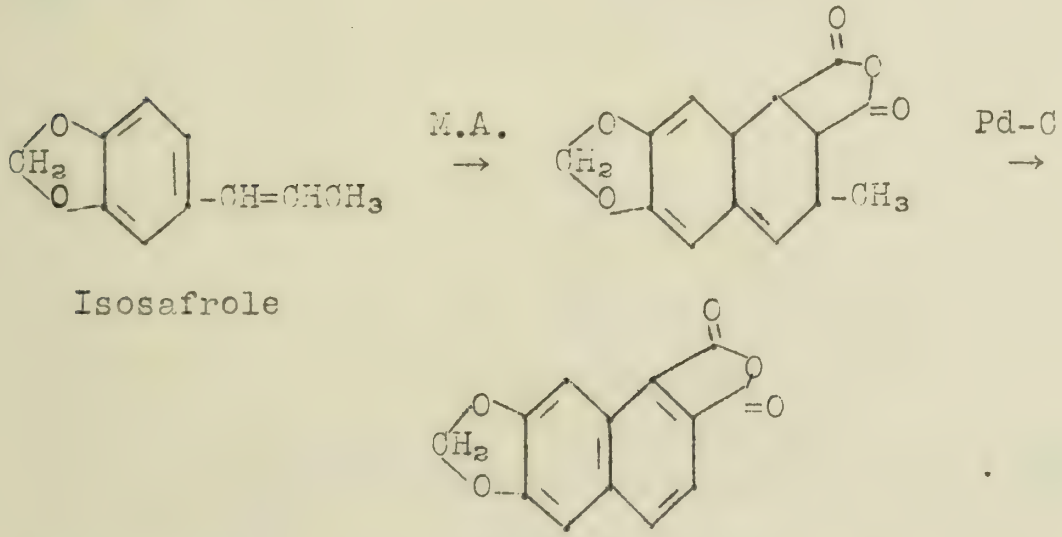
Certain phenanthrylethylenes undergo the Diels-Alder reaction to form adducts containing only one molecule of maleic anhydride (7).



R= $-CH=CHCH_3$; $-C=CH_2$ (CH_3); $-CH=CHC_6H_5$

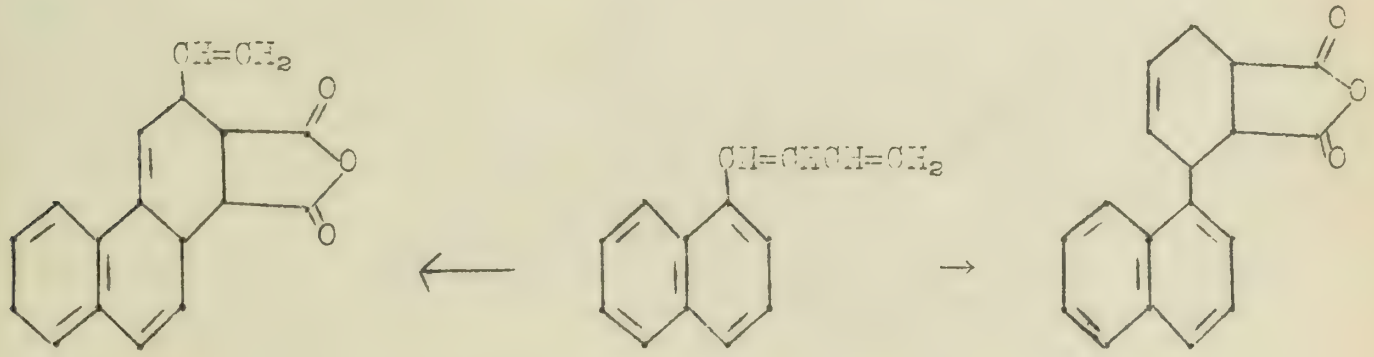
No adduct was obtained with 9-(α-phenylvinyl)phenanthrene, which behavior is similar to that of the diarylethylenes in which the ortho position is blocked.

Isosafrole, isoeugenol and anethole were treated with maleic anhydride by Hudson and Robinson (8). Anethole failed to react in the expected manner, but crystalline adducts were formed from the other two compounds. Example:

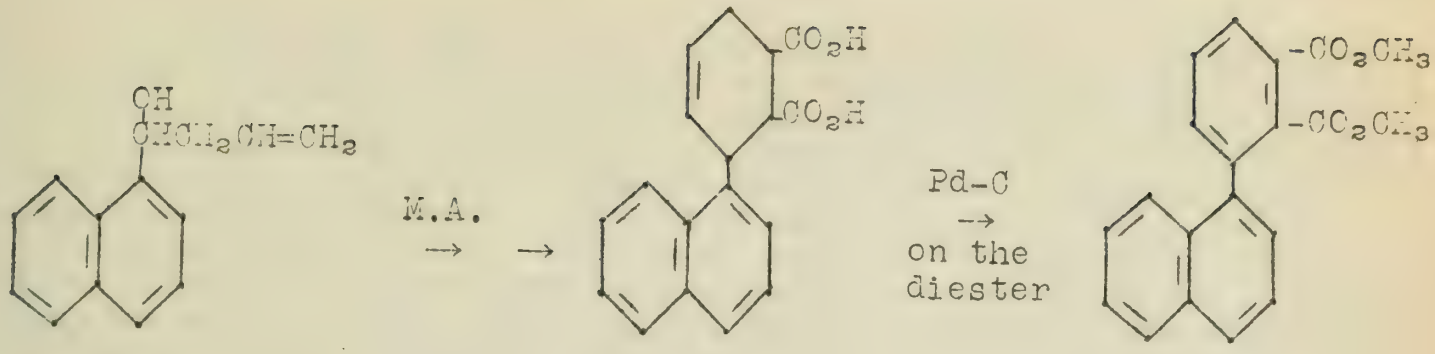


These authors conclude that an alkoxy group in the para position enhances the anionic character of the styrene system, and hence promotes the reaction with maleic anhydride. However, neither a para-methoxyl group nor a meta-methoxyl group alone will aid in the formation of a monomeric adduct in the styrene system.

The reaction of 1-(α-naphthyl)butadiene with maleic anhydride illustrates the relative reactivities of a diene system involving an aromatic double bond and a system which is completely aliphatic (9).



The reaction proceeded exclusively as follows:



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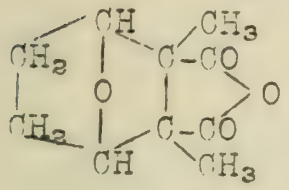
Reported by Roger Tull
January 16, 1947

SYNTHESIS OF CANTHARIDINE

Cantharidine, the active principle of Cantharis Vesicatoria (1) and of Mylabris Pustulata (2) was assigned structure I mainly on the basis of analytical evidence by Gadamer and others (3a, b,c,d,e). The crucial evidence in favor of I was provided by the isolation (4) of small amounts of dimethyl maleic anhydride on passing cantharidine over palladium asbestos at $> 280^{\circ}$. The anhydride must have been formed as a result of an inverce Diels-Alder reaction of the hypothetical dehydrocantharidine III. Conclusive evidence was, however, not forthcoming until the synthesis of desoxycantharidine (II) which has the same carbon skeleton as cantharidine was achieved (5).



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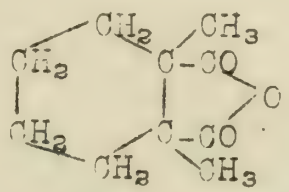
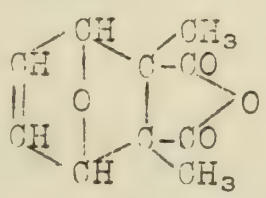
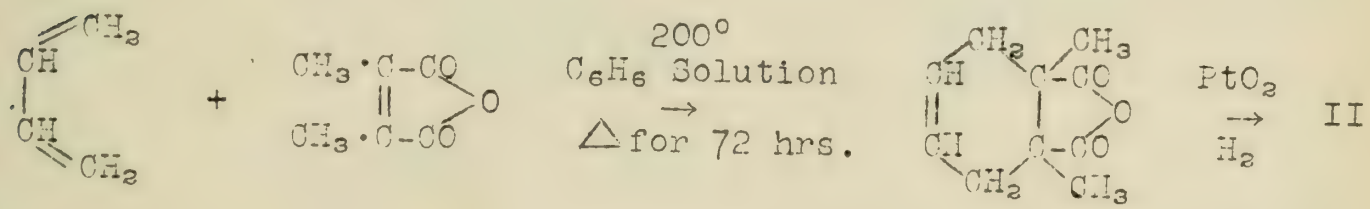


II



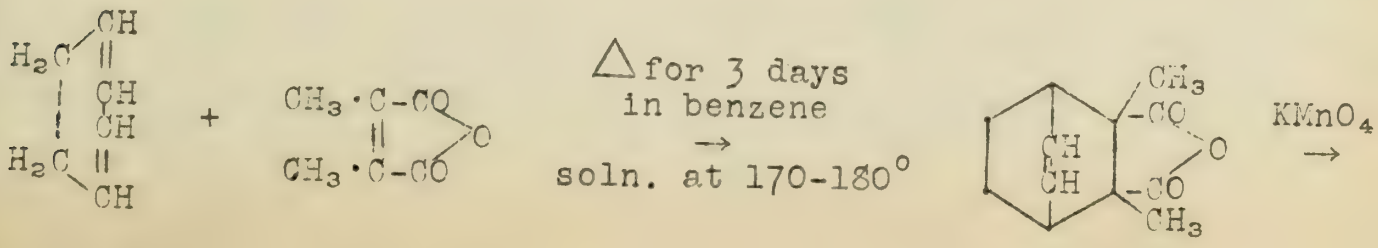
III

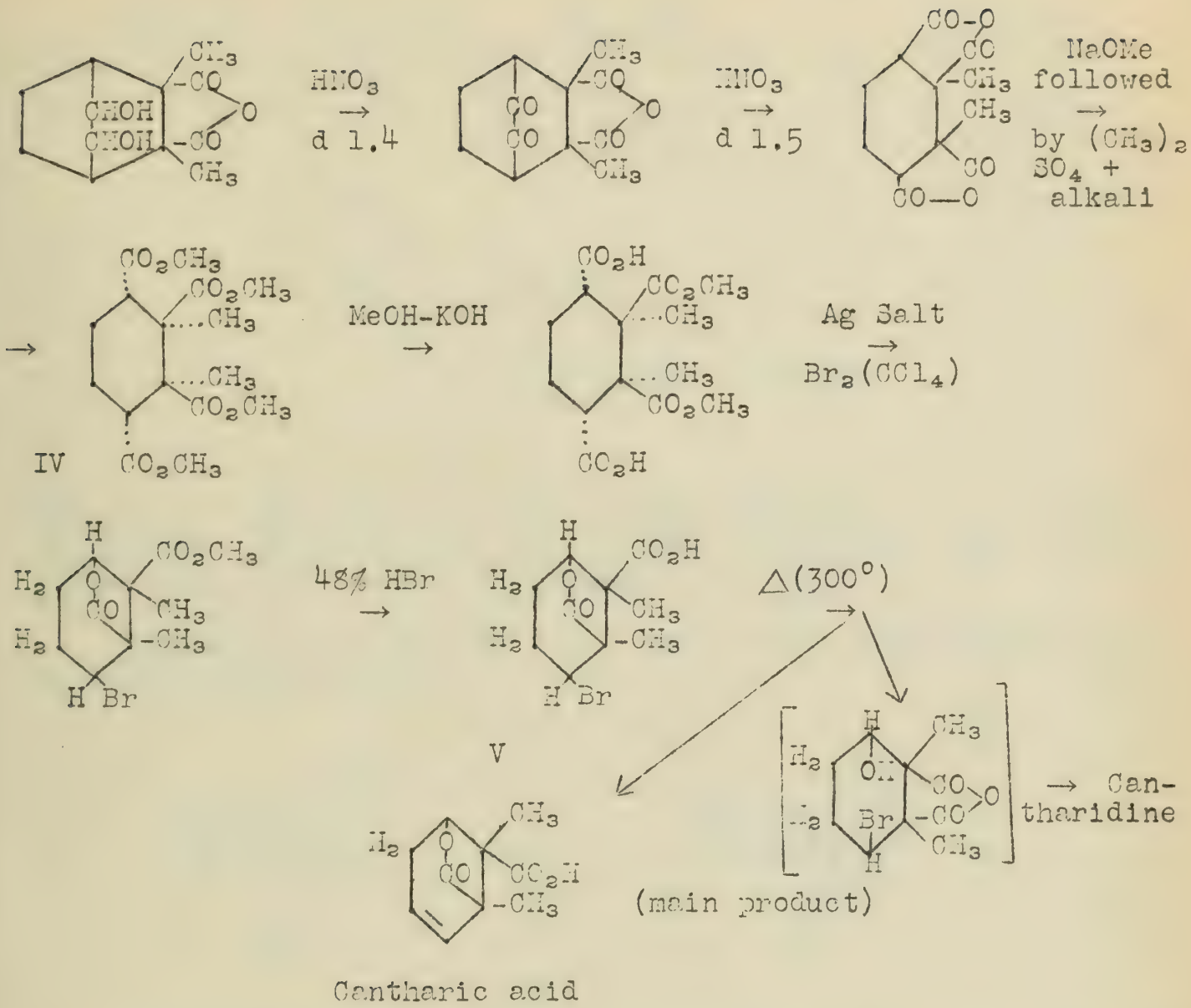
Woodward and Loftfield (5) synthesized cis-1,2-dimethyl cyclohexane-1,2-dicarboxylic anhydride as follows and proved its complete identity with desoxycantharidine obtained from the naturally occurring cantharidine.



The authors, although they did not furnish any direct proof that the synthetic anhydride had the cis configuration, pointed out that it, being identical with natural desoxycantharidine, must have the same configuration and desoxycantharidine as it is obtained from cantharidine by a series of reactions which cannot involve inversion has very likely the cis configuration of the latter (3d).

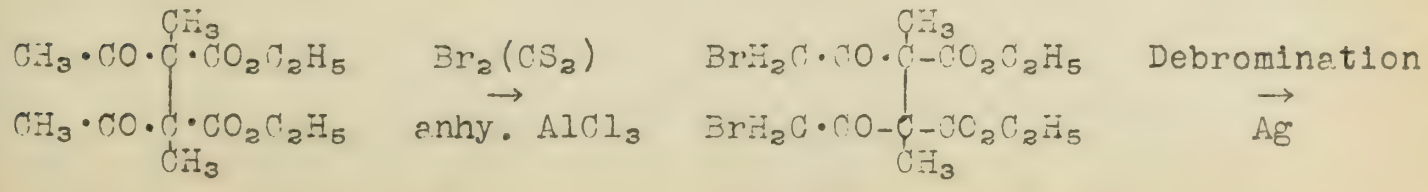
Ziegler, Schenck et al (6) employed the following rather complicated route and succeeded in synthesizing cantharidine.

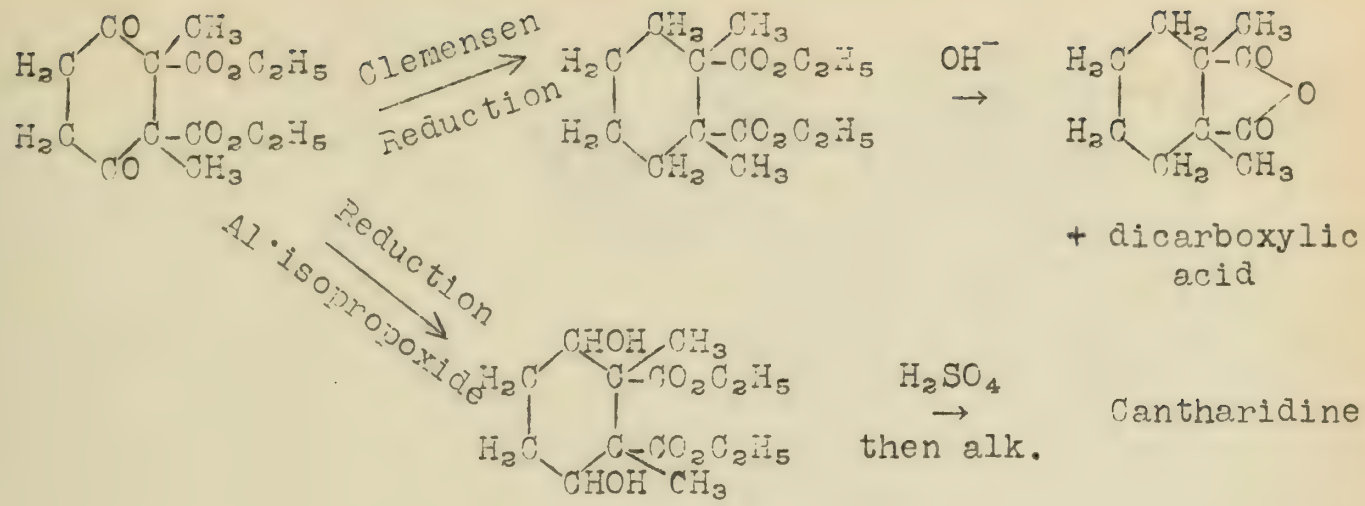




The conditions of esterification have to be carefully regulated in the preparation of IV as otherwise stereoisomers of IV are produced. Cantharidine is formed in such very low yields in the last step that physiological tests (formation of characteristic blisters) were employed for detecting it in the initial experiments. The authors later improved the method of isolation and succeeded in getting 50 mgm. of synthetic Cantharidine starting with 5 gm. of epi-hydrobromcantharic acid (V).

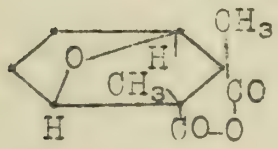
Another synthesis (7) was as follows:



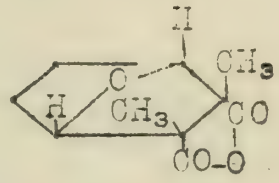


The yield on the basis of ethyl acetoacetate used was 10%. The synthetic product gave all the colomer reactions of natural cantharidine, did not depress the m.p. of an authentic specimen and formed the characteristic monophenyl hydrazone.

Woodward and Loftfield (loc. cit.) prefer configuration VII to VI for Cantharidine.



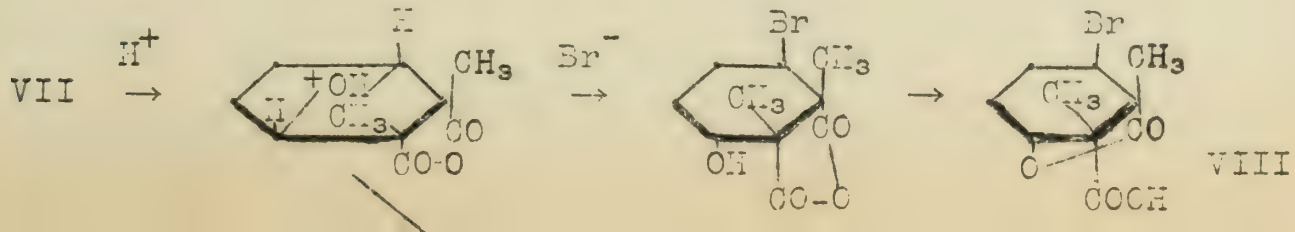
VI

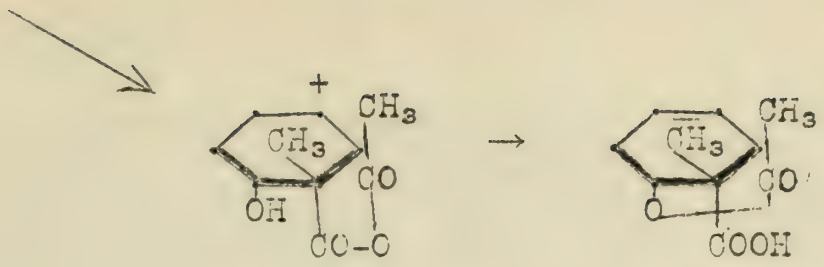


VII

P.T.O.

In VI the anhydride ring is endo while in VII it is exo with reference to the bridge oxygen. They interpret the action of bases (3b, 3c) on 3,6-dibromo-1,2-dimethylcyclohexane-1:2-dicarboxylic anhydride as evidence for VII. The loss of CO_2 and HBr in this reaction probably proceeds through an attack of the carboxylate ions on the backs of the carbons bearing the bromine atoms with the formation of an intermediate such as di-β-lactone. This means that the bromine atoms are on the opposite side of the ring from the carboxyls and since the oxido bridge was almost certainly replaced with inversion, it is concluded that the oxido bridge was originally on the same side as the anhydride ring. The formation of the lactones VIII and IX by the action of HBr on Cantharidine also seem to support VII.





IX

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   c) Rudolph, ibid., 254, 454 (1916).
   d) Gadamer, ibid., 252, 623, 660 (1914).
   e) Coffey, Rec. Trav. Chim., 42, 1026 (1923).
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Reported by S. Swaminathan
January 16, 1948

THE HYDROGENATION OF THE BENZENOID NUCLEUS

Pt black, Pt oxide, and colloidal Pt have been used successfully for the reduction of benzene and its derivatives. Glacial acetic acid is a good solvent (1); alcohol is excellent if small amounts of halogen acids are added. These speed up hydrogenation with a Pt oxide-Pt black catalyst (2).

Raney Ni, or Ni on kieselguhr are the most satisfactory catalysts, as they bring about the reduction of aromatic nuclei most rapidly, though pressures of 100 to 300 atm. are desirable.

Reactions: (3).--

I. Benzene and its simple mono alkyl derivatives reduce rapidly with Ni(R) or Ni(k) at 125-175° and under 100 atm., giving yields of 92-100%. In general, there is increased difficulty in hydrogenating the benzene ring with increased complexity of the molecule (1) (4a,b).

$$C_6H_5CH_3 \xrightarrow[\substack{175^\circ \\ 5\text{ min.}}]{Ni(R)} C_6H_{11}CH_3$$

II. Phenyl substituted methanes and ethanes reduce more slowly, the highly substituted ethanes requiring slightly higher temperatures.

$$(C_6H_5)_2CH_2 \xrightarrow[7\text{ hr. Ni(k)}]{150^\circ} (C_6H_{11})_2CH_2$$

$$(C_6H_5)_2CHCH(C_6H_5)_2 \xrightarrow[3\text{ hr. Ni(k)}]{175^\circ} (C_6H_{11})_2CHCH(C_6H_{11})$$

$$(C_6H_5)_3CH \xrightarrow[3\text{ hr. Ni(k)}]{200^\circ} (C_6H_{11})_3CH$$

III. Phenols reduce very rapidly at low temperatures (125-150°) and give almost quantitative yields with Ni(R) and Ni(k).

$$C_6H_5OH \xrightarrow[3\text{ hr. 100 atm.}]{150^\circ\ Ni(k)} C_6H_{11}OH$$

100%

$$C_6H_4(OH)_2 \xrightarrow{Ni(k)} C_6H_{10}(OH)_2$$

Resorcinol

<u>cis</u> and <u>trans</u>
90%

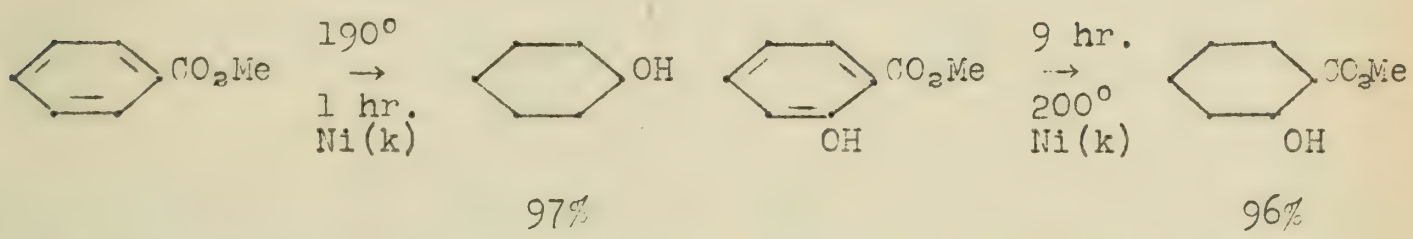
$$C_6H_5(OH)_2 \xrightarrow{Ni(k)} C_6H_{10}(OH)_2$$

Hydroquinone — <u>cis</u>

IV. Amino benzenes reduce very slowly, but give almost quantitative yields. Pressures of 200 to 300 atm. are desirable, but higher temperatures will give complete reduction at lower pressures. Reduction of primary amines usually leads to products containing some secondary amine. $2\ RNH_2 \rightarrow RNHR + NH_3$.

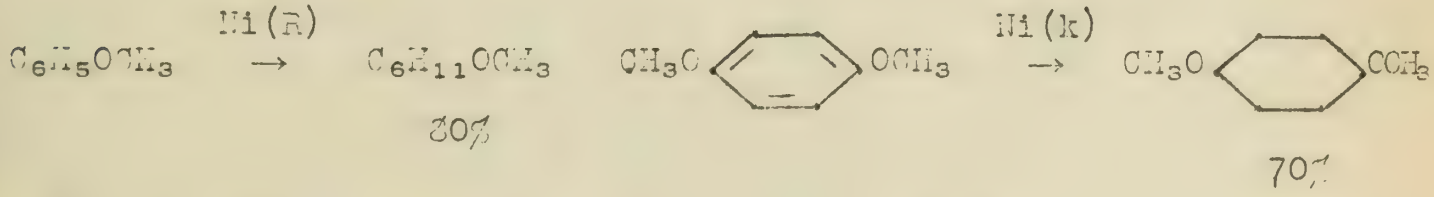
$$C_6H_5NH_2 \xrightarrow[9\ hr.\ Ni(k)]{175^\circ} C_6H_{11}NH_2 \quad 80\% \qquad C_6H_5NHC_6H_5 \xrightarrow[Ni(k)]{H} C_6H_{11}NHC_6H_{11}$$

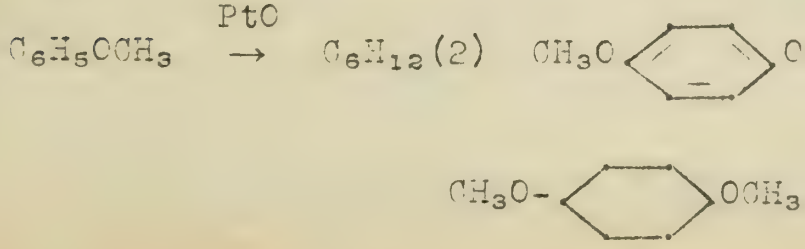
V. Carbethoxy groups distinctly retard hydrogenation of the benzene nucleus. However, 90-98% yields of the cyclohexane derivatives are obtained at 200°.



In the case of ethyl benzoate, hydrogenolysis occurs as well as hydrogenation.

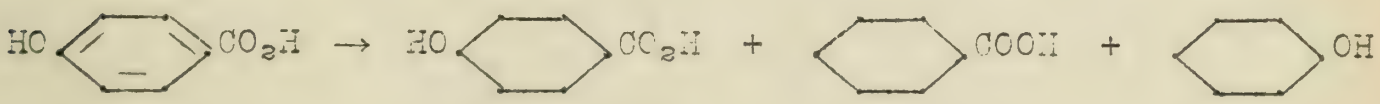
VI. Aryl ethers give lower yields (50-80%) because of hydrogenolysis.





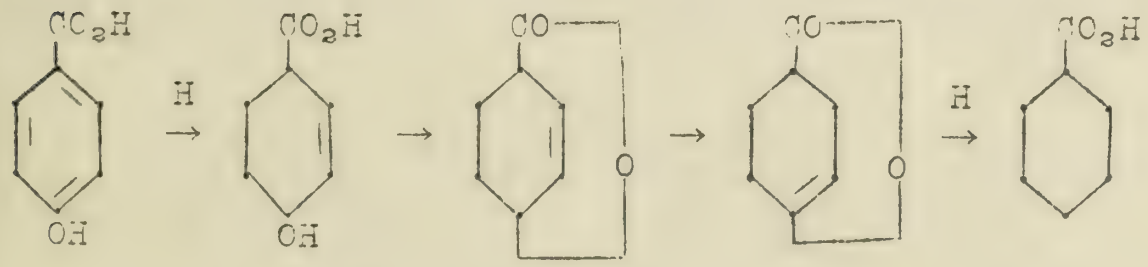
Aminophenols.--Senderens and Aboulec (5) reported that o- and p-aminophenol were reduced to the corresponding cyclohexanols, the ortho compound yielding a cis-trans mixture. They used a powdered Ni catalyst in alcohol. Skita and Rolfes (6) reduced o-, m-, and p-aminophenol hydrochloride with colloidal platinum in glacial acetic acid, but cyclohexylamine and dicyclohexylamine were the only products. Adams and Heckel (7) reduced several N-alkyl substituted m- and p-aminophenols with Pt oxide-Pt black in aqueous solution. The p-alkylaminophenols yielded N-alkyl substituted cyclohexylamines, and a cis-trans mixture of the p-aminocyclohexanol. The m- N-alkyl aminophenols gave similar results, but yielded only one isomer of the m-aminocyclohexanol. Of the substituted aminophenols, only the meta compound could be reduced under these conditions, yielding cyclohexylamine and dicyclohexylamine.

Hydroxy Benzoic Acids.--Edson, (8) using Pt oxide in water, obtained 20% of trans II, the remainder being III. From the meta acid, he obtained 60% of III, and a cis-trans mixture of II. The ortho acid yielded hexahydrosalicylic acid and 15% of cyclohexane carboxylic acid.



I II III IV

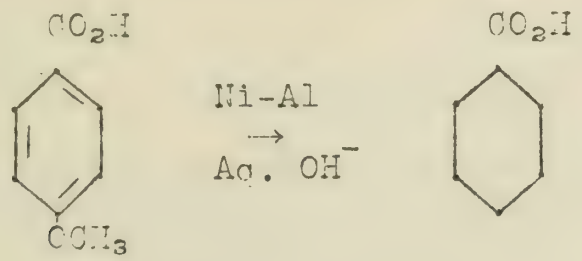
The postulated mechanism is the formation of a lactone. Thus the cis p-cyclohexane compound forms a lactone easily, and yields large amounts of III, and some trans II. The ortho hydroxy benzoic acid forms a lactone with difficulty, and yields little III. The meta hydroxy benzoic acid forms a lactone more easily, yielding cis-trans II, as well as III. The mechanism accepted by Edson was proposed by Jacobs and Scott (9).



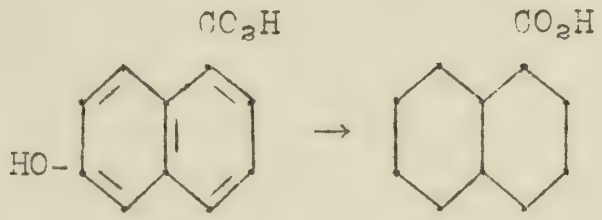
cis and trans

Hydrogenolysis does not occur through lactonisation, according to Levin and Pendergrass (10), although the fact that acid speeds

the reaction and increases the production of cyclohexane carboxylic acid whereas alkali slows the reaction and increases the cyclohexanol carboxylic acid produced, seems to indicate lactone formation. They favor direct displacement of the hydroxyl group, followed by hydrogenation. Schwenk et al. (11) showed that methoxy groups can be displaced in o- and p-methoxy benzoic acid.

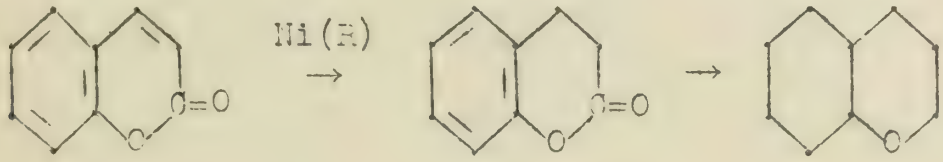


In the hydrogenation of 6-hydroxy-1-naphthoic acid (12)(13), the hydroxyl group was lost.



Acetylation or methylation of the hydroxyl group, variation of the temperature, change of reagent concentration, and esterification of the carboxyl group did not prevent hydrogenolysis of the hydroxyl group.

Formation of Aryl Ethers.--In 1940, Benneville and Connor (14) suggested that the formation of aryl ethers over Raney Ni might be characteristic of either lactones or aryl esters. They hydrogenated coumarin over Raney Ni and obtained a cyclic ether by complete reduction of the carbonyl group, an unusual reaction for this catalyst.



The authors suggested three mechanisms for the reaction, including a ring closure catalyzed by Raney Ni. Other examples of the formation of aryl ethers over Raney Ni are the reductions of γ-butyrolactone and γ-valerolactone, yielding 9% tetrahydrofuran and 17%

α-methyltetrahydrofuran respectively. In 1941, (15) it was shown that formation of a cyclic ether could not be attributed to coumarin as an aryl ester.

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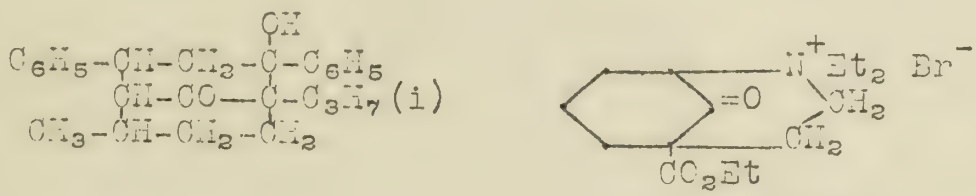
Reported by M. Rothstein
January 16, 1948

CARBONYL BRIDGE COMPOUNDS

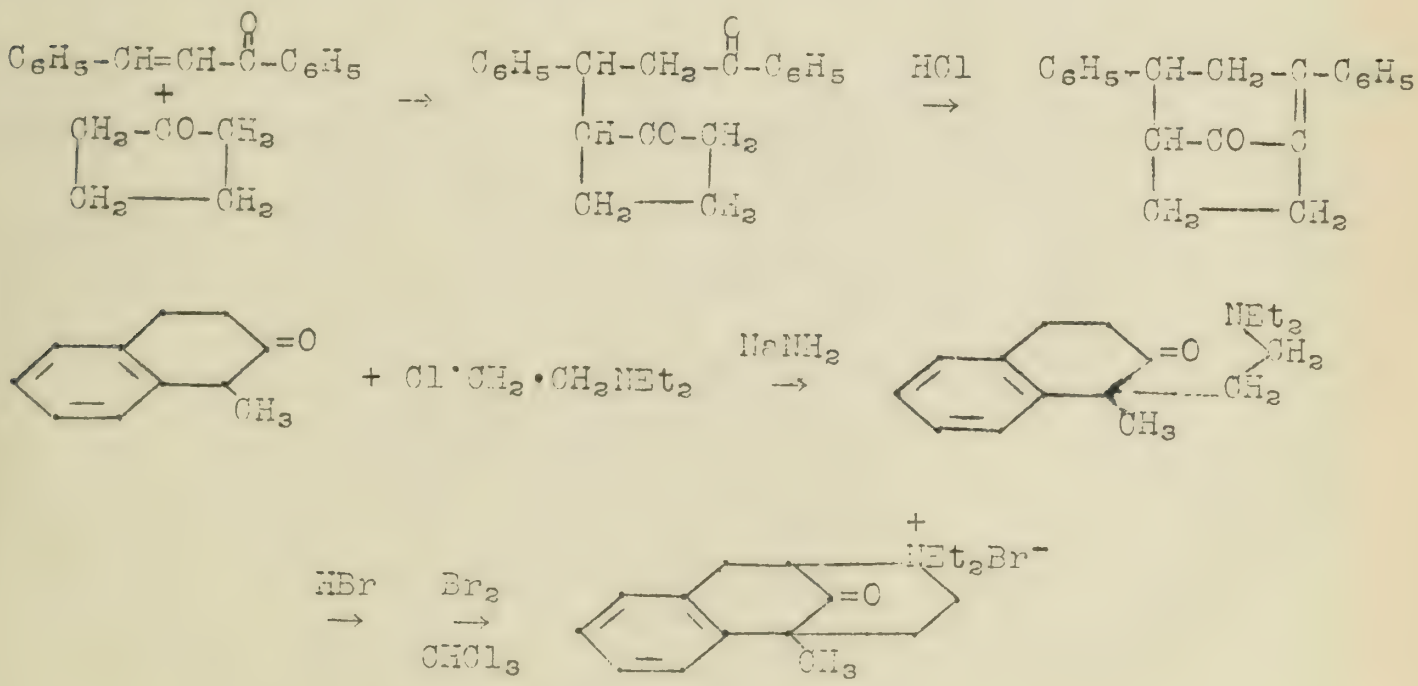
Alicyclic compounds containing a chain of atoms not connected to adjacent atoms in a carbon ring have long been known, but until the advent of the diene synthesis the available varieties were limited almost entirely to the terpenes and their derivatives. Many such bridged compounds, with a carbonyl group as the bridge, have been studied recently. For convenience these compounds have been called "carbonyl bridge compounds".

They may be classified in two general groups; those in which the ring is saturated and those containing an ethylenic linkage. They may be further subdivided according to the size of the ring.

Synthesis of representative carbonyl bridge compounds.--Only a few compounds, containing saturated rings with established structures, are reported in the literature (1,2).

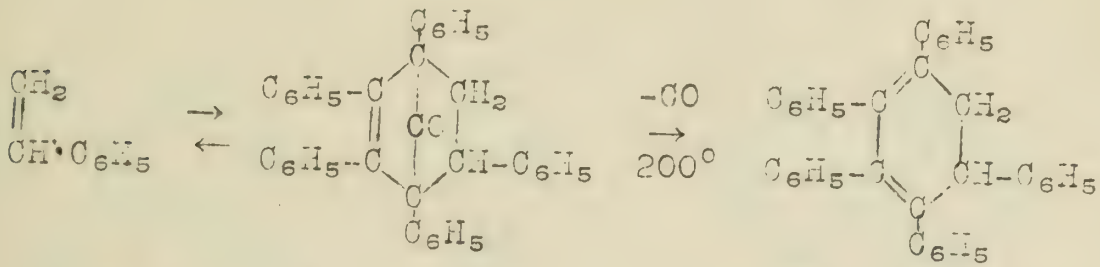


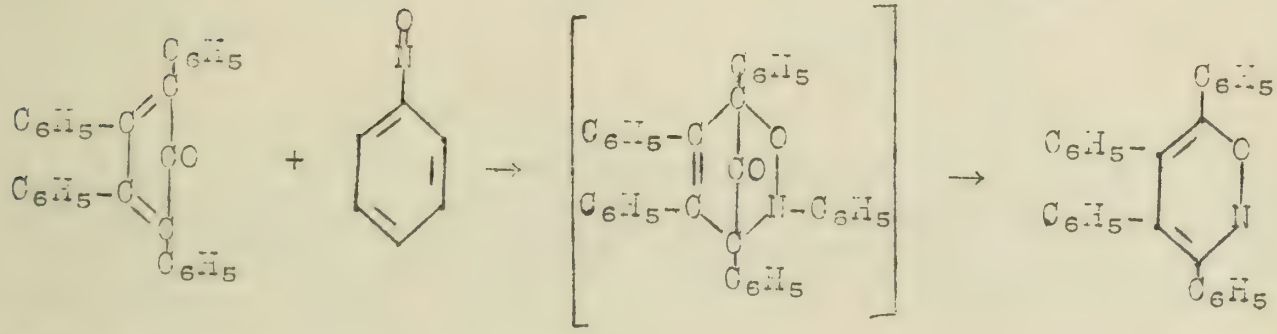
There are only a few bicyclic ring systems known having more than six carbon atoms in the ring and containing both an ethylenic linkage and a carbonyl bridge (1,2).



Many of the large number of six-membered multicyclic ring systems having a carbonyl bridge have been made available by the diene synthesis from cyclopentadienones and appropriate olefinic

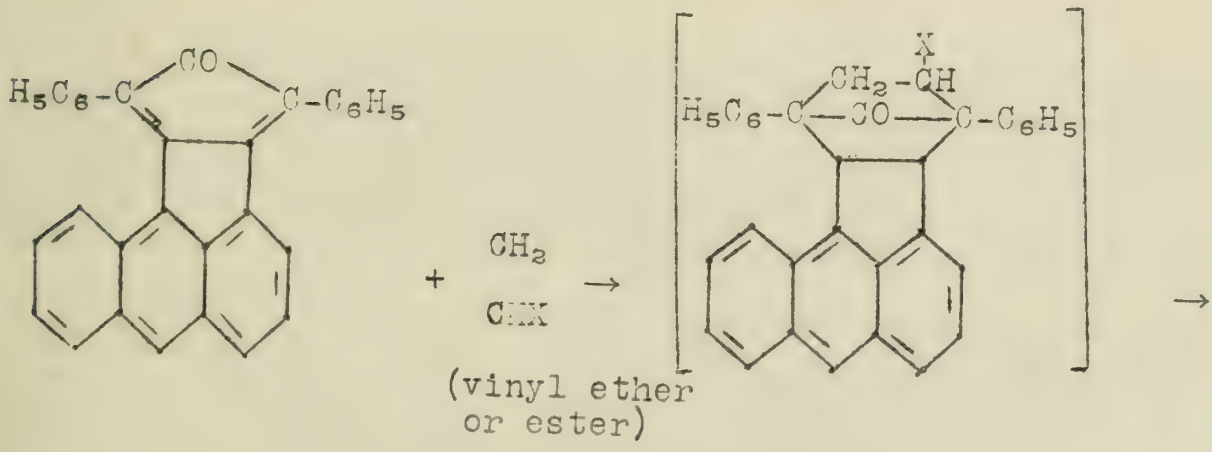
compounds. The reaction is limited by (1) the available cyclpentadienones and (2) the unsaturated addends. Two examples of addition reactions follow (3,1).

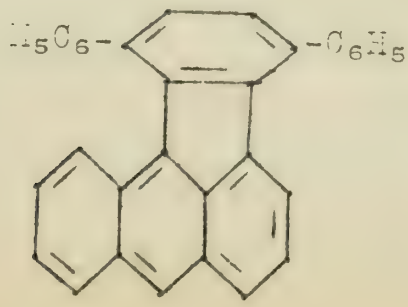


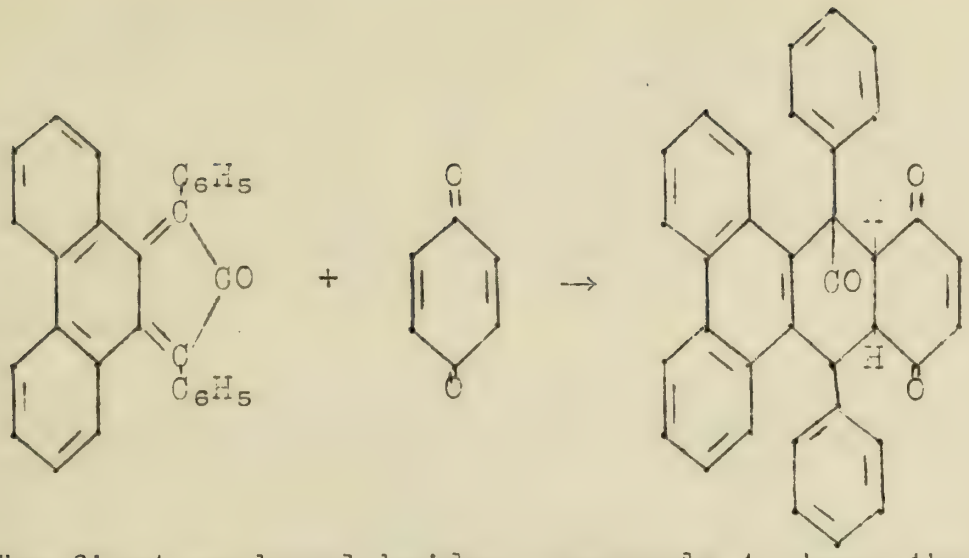


Other addends which have been used are β-nitrostyrene, allyl alcohol, allyl chloride, maleic anhydride, fumaric and maleic esters, and acetylenic compounds.

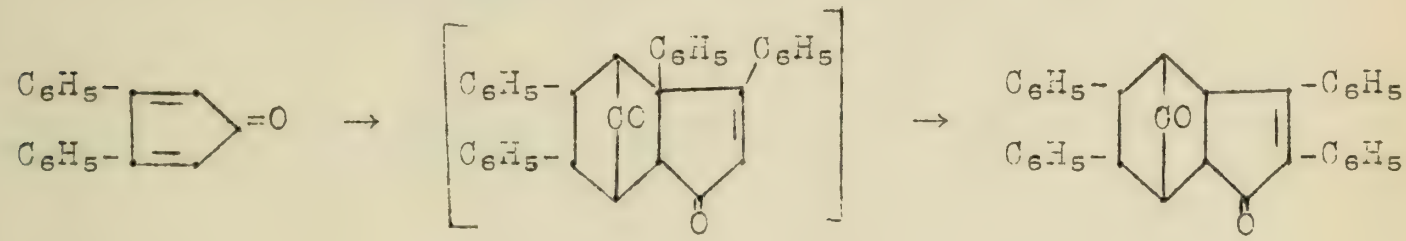
Polynuclear highly arylated aromatic compounds may be obtained in a similar fashion. Examples are given below (3,1).





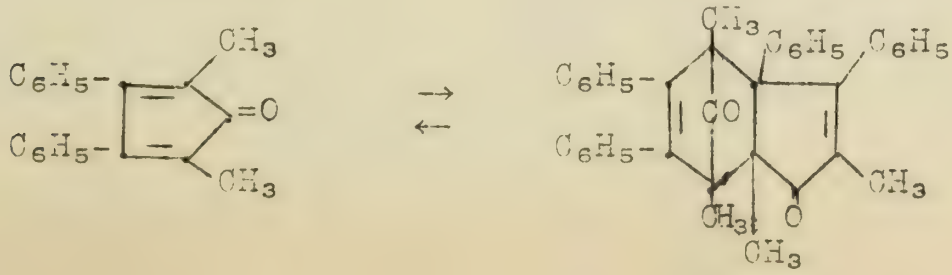


The first carbonyl bridge compounds to have their structures elucidated were the indenes and related compounds. These are obtained by the dimerization of cyclopentadienones. For example, anydroacetonebenzil dehydrates to diphenylclcyopentadienone which dimerizes as shown.



In the final product, the angular phenyl group has migrated to the 2-position. The available evidence on angular phenyl groups in these compounds indicates that they show a great tendency to migrate when this is possible, but there is as yet, no single instance of a shift involving the displacement of any atom or group other than hydrogen. Proof for such a rearrangement has been obtained (4).

Other bimolecular products, formed by the dimerization of cyclopentadienones, are known, but they must have structures as represented below, since they all dissociate to varying degrees in solution or when heated, hence there have been no rearrangements. Experimental evidence for the presence of the angular phenyl group in these compounds has been obtained (5).

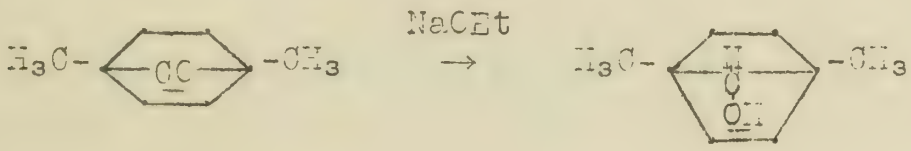


Properties of carbonyl bridge compounds.--The few known seven- and eight-membered unsaturated bicyclic ring systems having a carbonyl bridge do not exhibit any unusual properties and they are not altered on heating. The most conspicuous property of the carbonyl bridge compounds having a six-membered ring and an ethylenic linkage is their behavior when heated - the bridge is split out as CO. This "decarbonylation", which is usually quantitative, is rapid at 200-220° and in favorable instances can be detected at 75-80°. The other product is usually a dihydrobenzene derivative, but occasionally this is dehydrogenated to the corresponding aromatic compound.

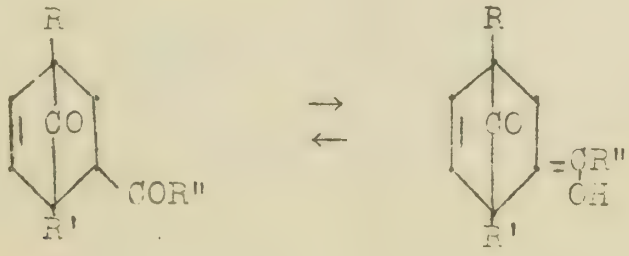
Certain conclusions can be drawn as to the course of the reaction that may be expected between carbonyl bridge compounds and alkaline reagents (6). They are as follows:

(1) If there are phenyl groups at the ends of the bridge, the latter is cleaved at one end, so that the product is a carboxylic acid.

(2) If there are methyl groups at the ends of the bridge, reduction to a carbinol takes place.



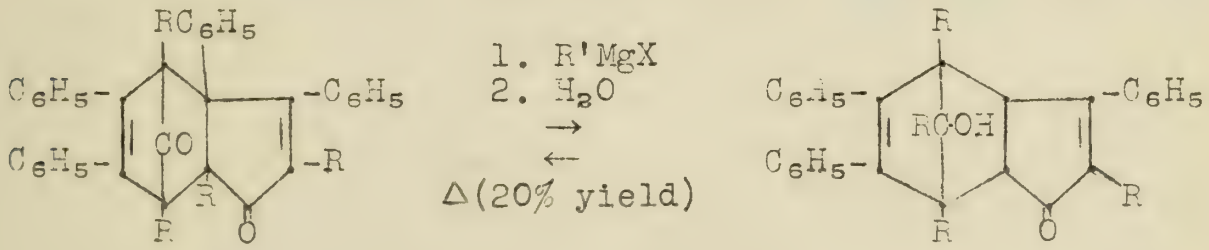
(3) If there are methyl groups or hydrogen at one or both ends of the bridge, and a side chain containing an unsaturated linkage of such a nature that upon enolization a double bond can be formed between the ring and the side chain, all possible types of reaction may be expected. The keto group in the side chain may be reduced to give a carbinol.



The action of the bimolecular products from the anhydroacetone-

benzils or their dehydration products with organomagnesium compounds has recently been studied (7). From this study, it was possible to arrange the bimolecular products in three groups: (1) those derived from symmetrical dialkylated anhydroacetonebenzils, (2) those derived from monoalkylated homologues, and (3) those from anhydroacetonebenzil itself. Members of the last two groups show one active hydrogen and one addition when treated with CH_3MgI, whereas in the first only addition can be detected. The reactions are summarized below.

1.



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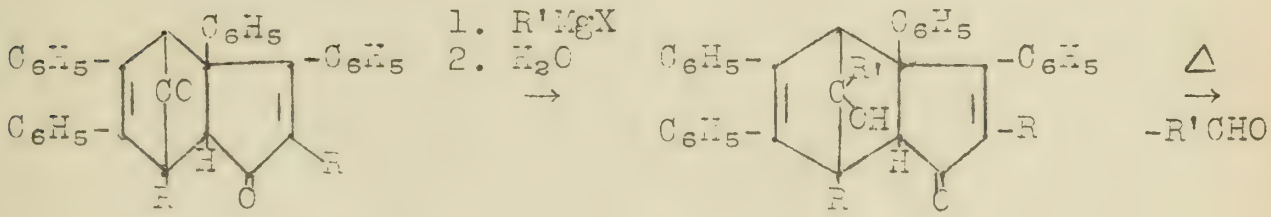

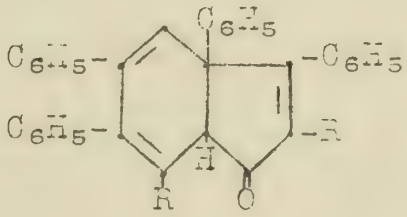

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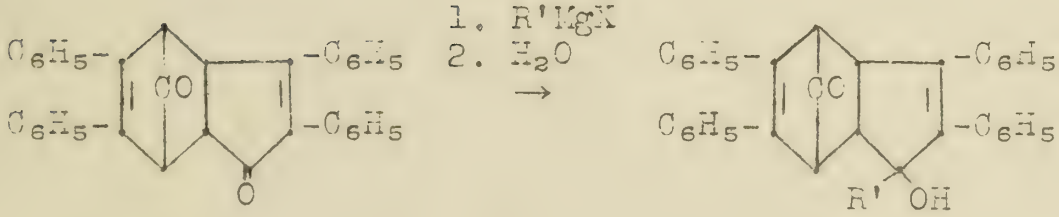

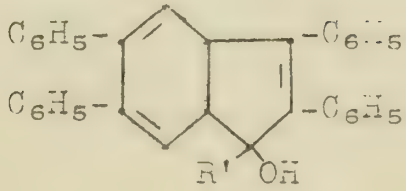

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Reported by Emmett H. Burk, Jr.
January 23, 1948

ALKOXYMERCURATION

Alkoxymercuration is the addition of a mercuric or basic mercuric salt to an olefinic linkage in alcoholic solution to give a product of the type RO-C-C-HgX. In aqueous solution the R is replaced by H. The reaction takes place at room temperature, sometimes requiring a catalyst.

The instability of the product in even dilute mineral acids led some investigators (1,2) to postulate a molecular complex of the type $>C=C<\ \cdot Hg(OR)X$, rather than a true addition compound, but this failed to account for many of its reactions.

$$RO\text{-}\overset{|}{C}\text{-}\overset{|}{C}\text{-}HgX + HX \rightarrow \;>C=C< + ROH + HgX_2 \qquad (1)$$

whereas

$$RHgX \xrightarrow[HX]{\text{hot, conc.}} RH + HgX_2 \qquad (2)$$

But

$$ROCH_2CH_2HgX \xrightarrow{I_2} ROCH_2CH_2I \qquad (3)$$

$$\underset{OR\ HgX}{\phi CH\text{-}CH}\text{-}COOMe \xrightarrow[\text{or } Na_2S_2O_3]{H_2S \text{ in alk. } NH_3} \underset{OR}{\phi CH}\text{-}CH_2\text{-}COOMe \qquad (4)$$

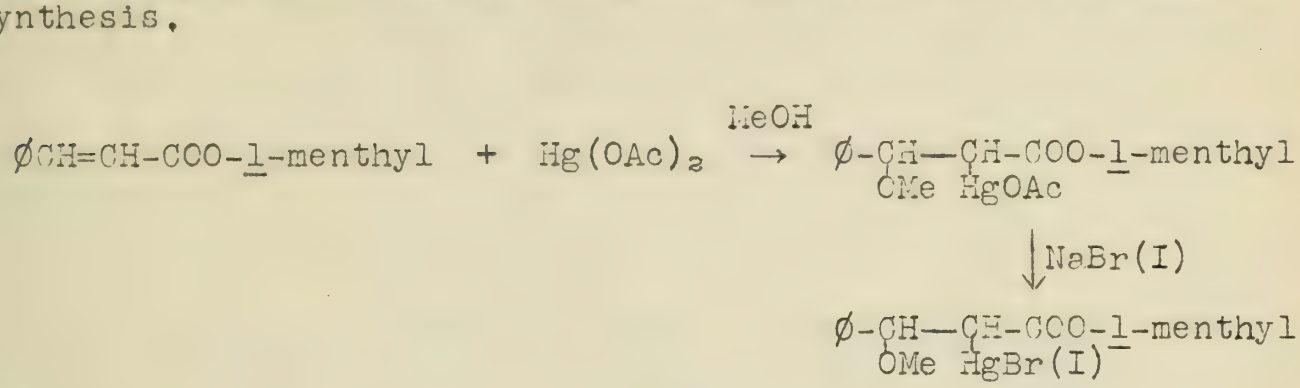
$$\underset{OR\ Hg\text{-}O}{R'CH\text{-}CH}\text{-}C=O \xrightarrow[NaOH]{H_2S} \underset{OR}{R'CH}\text{-}CH_2COOH \qquad R'=\phi,\ CH_3 \qquad (5)$$

$$HOCH(R)CH_2HgX \xrightarrow[\text{or electrolysis}]{Na\cdot Hg} CH_3\text{-}CH(R)OH \qquad R=CH_3,\ H \qquad (6)$$

All known complex organic mercury salts are of the type $A\cdot HgX_2$ rather than $A\cdot Hg(OR)X$.

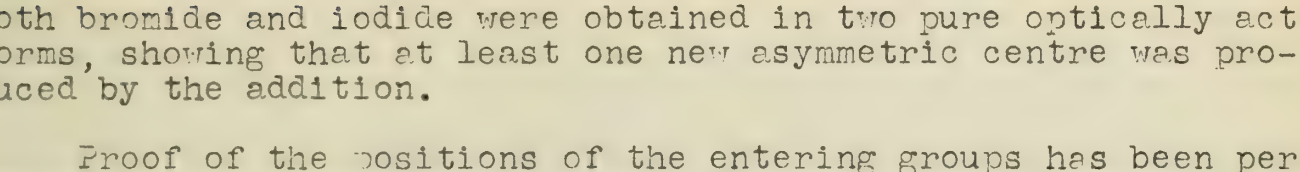
In support of a true addition compound , Adams, Roman and Sperry (3) found that the product formed from o-allylphenol was stable to acid, and could be formed by reaction with mercuric chloride whereas usually the basic mercuric chloride is required. Mercuric acetate, however, will add directly to olefins since the products are stable toward the acetic acid formed.

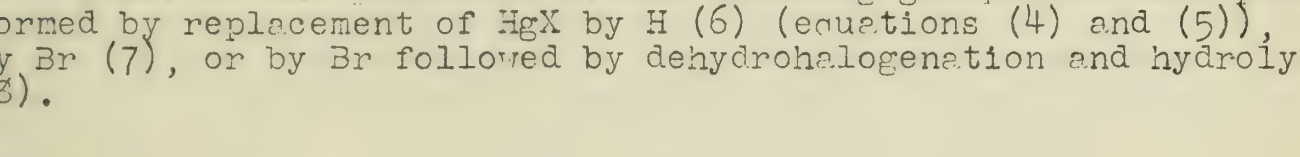
Marvel and coworkers (4,5) proved conclusively that the product was a true addition compound by means of an asymmetric synthesis.



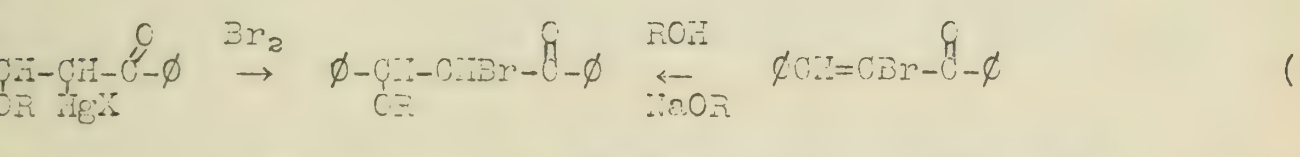
Both bromide and iodide were obtained in two pure optically active forms, showing that at least one new asymmetric centre was produced by the addition.

Proof of the positions of the entering groups has been performed by replacement of HgX by H (6) (equations (4) and (5)), by Br (7), or by Br followed by dehydrohalogenation and hydrolysis (8).





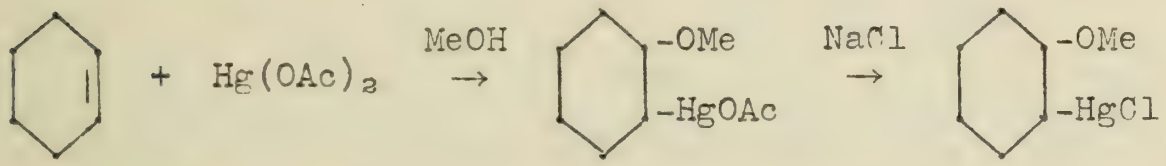
Wright (8,9) studied the methoxymercuration reaction in more detail to determine the mechanism of addition. He proposed two mechanisms:



The first of these was supported by kinetic studies carried out in a large excess of alcohol solvent since 1) the reaction is second order in mercuric acetate and olefin, and 2) the alcohol used affects the rate. In all cases studied only one of the two possible diastereomeric forms was produced, and when both members of a cis-trans pair of olefins were used each gave rise to a different diastereomer, thus indicating that RO-HgOAc adds as a unit rather

than as ionic or free radical fragments. The addition is inhibited by cyanide and pyridine, both electron donors, and catalyzed by peroxides and boron trifluoride, electron acceptors. The catalyst is used up during the reaction, and it was found that each catalyst is not effective for all olefins.

Of interest recently (10) has been the addition product of cyclohexene.

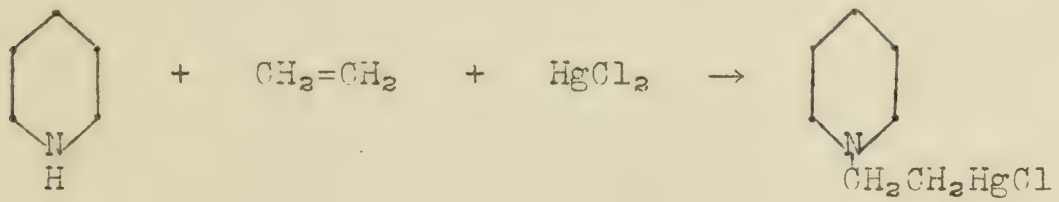


(9)

This α-1-chloromercuri-2-methoxycyclohexane can be isomerized to a β-form by refluxing in alcoholic solution in the presence of a catalyst such as benzoyl peroxide, hydrazine hydrate or biphenyl mercury, and further treatment with acetic acid and aqueous sodium chloride. The isomerization is believed to go through the R_2Hg compound, thus breaking the C-Hg bond and changing the configuration about carbon atom 1. By using l-mercuric lactate in place of mercuric acetate, an asymmetric synthesis was achieved, producing an optically active α-form which was isomerized to an active β-form without racemization.

Methoxymercuration may find uses in the determination of gaseous olefins in the presence of paraffins (11), of cis-trans configurations (12), and of the amounts of cis and trans olefin in a mixture (13). The last two are based on the fact that the rate of addition to a cis isomer is greater than to a trans.

Recently Freidlina and Kotschetkova (14) have carried out a similar reaction, replacing the alcohol by an amine.



The product, however, has quite different properties, giving no reaction with H_2S, alkali or boiling mineral acid, and decomposing to give ethylene upon heating or when treated with potassium cyanide or excess sodium iodide in alcohol.

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Reported by Elizabeth J. Underhill
January 23, 1948

KETONE SYNTHESIS USING ORGANOCADMIUM REAGENTS

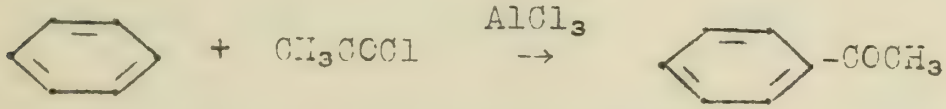
In 1936 Gilman and Nelson (1) suggested the use of organocadmium reagents for the general preparation of ketones. Because of recent work, this method may now be regarded as one of the best and most widely applicable procedures for laboratory preparation of ketones. The synthesis involves the following reactions:

$$RBr + Mg \rightarrow RMgBr$$
$$2RMgBr + CdCl_2 \rightarrow R_2Cd + MgBr_2 + MgCl_2$$
$$R_2Cd + 2R'COCl \rightarrow 2RCOR' + CdCl_2$$

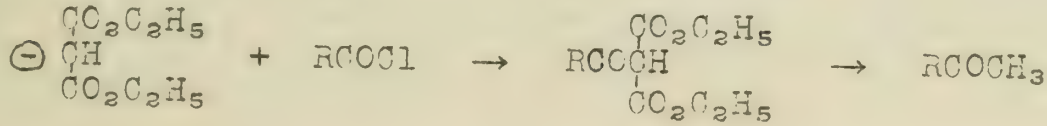
This sequence of reactions requires only a few hours without isolation of intermediates and yields are usually good.

Experimental Procedure (2,3).--Solid cadmium chloride is added to the Grignard reagent and the mixture refluxed until a negative Gilman test (4) for Grignard reagent is obtained (20-50 min.). The ether is then removed by distillation and the reaction with acid chloride is carried out in benzene. The organometallic complex is decomposed with acid, and the separated benzene layer is distilled to obtain the ketone. Yields are usually 60-85%. With a large excess of cadmium reagent yields up to 98% have been obtained (5).

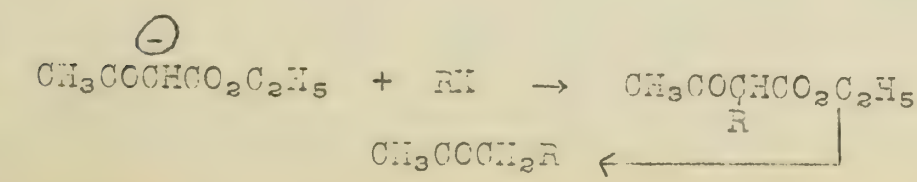
Comparison with Other Methods.--The most useful methods for preparing ketones involve a Friedel-Crafts reaction, an enolate condensation or some type of Grignard reaction.

(1) 

Useful for aromatic compounds containing no meta-directing groups; only certain orientations may be obtained.

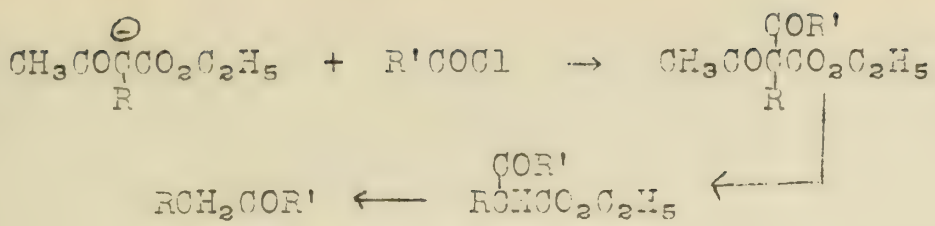
(2) 

Good method for methyl ketones.

(3) 

Involves two separate operations; yields not high.

(4)



A lengthy procedure; yields are not particularly good.

(5) $RMgX + R'CN \rightarrow R'\underset{R}{C}{=}NMgX \rightarrow RCOR'$

$RMgX + R'CONH_2 \rightarrow R'-\overset{R}{\underset{OMgX}{C}}-NR_2 \rightarrow RCOR'$

Yields are very good if there is no other Grignard-reactive functional group present.

(6) $RMgX + (CH_3CO)_2O \xrightarrow{-70^\circ C} RCOCH_3$

Good general method for methyl ketones; secondary and tertiary alkyl halides can be used satisfactorily.

(7) $(RZnCl \text{ or } R_2Zn) + R'COCl \rightarrow RCOR'$

Identical with the cadmium method but yields are poorer and the reagent is more difficult to prepare (1,5).

Scope and Limitations of the Method. The Organic Halide.--Alkyl bromides give better yields than the chlorides or iodides (1,2). Aromatic ketones can be prepared in good yield, but if an alkyl halide is used, it must be primary. This is the chief limitation of the method.

The Acid Chloride.--Both aromatic and aliphatic acid chlorides react smoothly. Some of the acid chlorides that have been used satisfactorily are: high molecular weight aliphatic (1), sterol (5,6,7), α-chloro (2), cyclohexyl (8), and half-ester acid chlorides (2). Yields are lower with acid anhydrides (9).

Side Reactions.--The cadmium reagent may react with the enol form of the ketone being prepared, particularly if enolization is promoted.

Since acid chlorides react with diethyl ether in the presence of anhydrous magnesium halide, some ester is obtained if the reaction is carried out in ether. If the ether is distilled off and the reaction with acid chloride is carried out in benzene, very little ester is formed.

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Reported by Robert D. Rands
January 23, 1948

RECENT WORK ON SILICON-BEARING ORGANIC COMPOUNDS

A New Method for Producing the Carbon-Silicon Bond.--A new method has been reported for producing carbon-silicon bonds. Generally the method may be written.

$$RCH{=}CH_2 + HSiCl_3 \xrightarrow[\text{or U.V.}]{\text{Peroxide}} RCH_2CH_2SiCl_3 \qquad (1)$$

This reaction seems to be closely related to the following free radical reaction reported by Karasch (4).

$$RCH{=}CH_2 + HCCl_3 \xrightarrow[\text{or light}]{\text{Peroxide}} RCH_2CH_2CCl_3 \qquad (2)$$

The following two examples given by Whitmore (1) indicate the general method.

1. 1-Octene (1/3 mole) and trichlorosilane (1 mole) are reported to give a 99% yield of n-octyl trichlorosilane after 9 hours at 50-63° in a nitrogen atomosphere using diacetyl peroxide (0.025 moles) as a catalyst.

2. If, in the above example, U. V. light replaces the diacetyl peroxide the yield of n-octyltrichlorosilane is 24%.

Burkhard and Krieble (2) used a slightly higher ratio of olefin to trichlorosilane at temperatures of 70-100° for 4-24 hours. The higher temperatures and the nature of their reactants made it necessary for them to run their reaction in a citrate bottle or in a glass-lined autoclave. Pressures were not reported. With these conditions the yields of various alkytrichlorosilanes are generally not as good as that reported by Whitmore for n--octyltrichlorosilane A summary of the findings of Burkhard and Krieble may be outlined as follows:

1. In contrast to CCl_4, $SiCl_4$ will not react.

2. Nearly all olefins will react. Examples given are 1-pentene, cyclohexene, allyltrichlorosilane, vinyltrichlorosilane, isobutylene, and acetylene. With regard to isobutylene it is noteworthy that Karasch (5,6) reported that compounds of the type $R_2C{=}CH_2$ would not react in his reactions.

3. One or two of the chlorines of trichlorosilane may be replaced by alkyl groups, but the yields are poorer. Examples cited are methyldichlorosilane and di-n-propylchlorosilane.

4. From the various olefins more or less high boiling or polymeric material was formed. In fact, with styrene, only polymers containing some silicon and chloride were obtained. In considering this fact Burkhard and Krieble pointed out that the Karasch (4) mechanism allows for two possible routes.

$$RCH{=}CH_2 + Cl_3Si\cdot \rightarrow RC\dot{H}CH_2SiCl_3$$

$$RC\dot{H}CH_2SiCl_3 \xrightarrow[\text{I}]{HSiCl_3} RCH_2CH_2SiCl_3 + Cl_3Si\cdot \qquad (3)$$

$$RC\dot{H}CH_2SiCl_3 \xrightarrow[\text{II}]{RCH{=}CH_2} RC\dot{H}CH_2\overset{R}{C}HCH_2CH_2SiCl_3$$

Route I is a chain transfer reaction and route II is a polymerization reaction. Evidently, the major product is determined by the relative rates of these reactions.

Other workers (3) have reported that if the temperature and pressure are high enough no catalyst needs to be added. There is no mention made of excluding air from their reactants so that it is possible that their reactions are really peroxide catalyzed. They have reacted a number of olefins with $HSiCl_3$ at temperatures from 160° (reaction slow) to 400° (decomposition starts) for about 18 hours to give good yields of alkyltrichlorosilanes. The actual pressures used in their reactions were dependent upon such things as the nature of the reactants and products, the maximum temperature, and the time required to reach the maximum temperature. An example is given for 1-octene and trichlorosilane. An excess of 1-octene was used. The temperature was raised to 300° over a 2-1/2 hour period and held at 300° for 18 hours. The maximum pressure was 276 p.s.i. obtained at 270°C. The yield of n-octyltrichlorosilane was 94%. These workers reported the use of the following olefins: 1-alkenes (C_2 to C_{18}), 2-butene, isobutylene. They used also a wide variety of alkyl and aryl silanes of the type $RSiHCl_2$ and R_2SiHCl. Tribromosilane was used, but the product from this silane was not described.

The mode of addition in this reaction is shown by three facts.

1. No hydrogen is evolved when the products are treated with sodium hydroxide. Thus there are no silicon-hydrogen bonds present in the product.

2. There is no loss of hydrolyzable halogen during the reaction. Thus there are no silicon-chlorine bonds destroyed during the reaction.

3. Physical properties in cases in which the compound was previously known compare favorably.

Some New Organic Derivatives of Silicic Acid.--Some new organic derivatives of silicic acid have been reported (7). These have the general formula $(RO)_{4-X}SiX_X$ where RO- is a t-alkoxy group and X may be chlorine, amino, hydroxy, or alkoxy. The following reactions illustrate the method of preparation and some of its possibilities.

$$2(CH_3)_3COH + SiCl_4 : 2C_5H_5N \rightarrow [(CH_3)_3CO]_2SiCl_2 + 2C_5H_5N{\cdot}HCl \quad (4)$$

80% yield

By the proper choice of conditions it is possible to replace one, two, three, but not four chlorines of silicon tetrachloride with t-alkoxy groups. The best yields are obtained most easily when two chlorines are replaced.

$$[(CH_3)_3CO]_2SiCl_2 + H_2O \xrightarrow[\text{cooling}]{XsNH_3} [(CH_3)_3CO]_2Si[OH]_2 \quad (5)$$

60% yield

$$[(CH_3)_3CO]_2Si[OH]_2 \xrightarrow{\text{heat}} \text{hard, brittle resin} + (CH_3)_3COH + (CH_3)_2C{=}CH_2 + H_2O \quad (6)$$

$$[(CH_3)_3CO]_2SiCl_2 + NH_3 \xrightarrow[\text{cooling}]{} [(CH_3)_3CO]_2Si[NH_2]_2 \quad (7)$$

80% yield

$$[(CH_3)_3CO]\ SiCl_3 + NH_3 \rightarrow \text{hard, brittle insoluble nitrogen containing resin} \quad (8)$$

$$[(CH_3)_3CO]_2SiCl_2 + 2ROH\ (\text{not tertiary}) \rightarrow [(CH_3)_3CO]_2Si[OR]_2 + 2HCl \quad (9)$$

$$[(CH_3)_3CO]_2Si[NH_2]_2 + 2ROH \rightarrow [(CH_3)_3CO]_2Si[OR]_2 + 2NH_3 \quad (10)$$

(not tertiary)

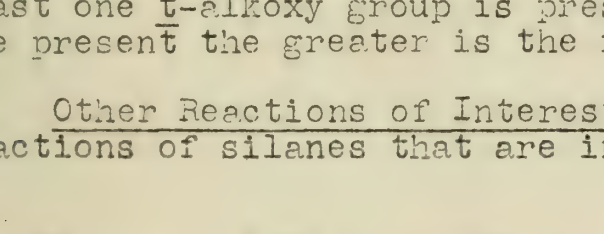
Some of these reactions are interesting because they give products which might not be expected when comparing them with known reactions. In the resinification reaction 6 the resin is formed

by splitting out alcohol between molecules and not water as would be expected. The resin appears to be

From the amination reaction 7 the diamino derivative is sufficiently stable to be distilled *in vacuo*. The only other similar reaction reported thus far is the reaction of trimethylchlorosilane with ammonia (8). This gives hexamethyl disilizane.

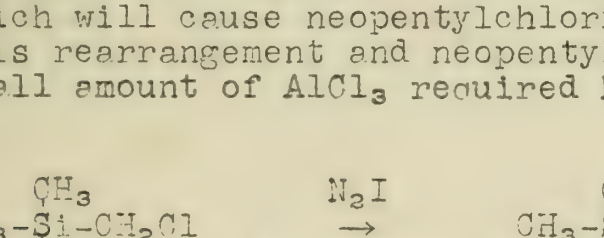
Mixed *ortho* and esters of the type formed in reactions 9 and 10 are interesting because of their resistance to acid and alkaline hydrolysis. This is illustrated by comparing the resistance to alkaline hydrolysis of tetra-*n*-butyl silicate and tri-*n*-butyl-*t*-butyl silicate. After heating 8 hours at 100° with 1. N sodium hydroxide, 1.5% of the former and 95% of the latter are recovered unchanged. This resistance to hydrolysis is evident whenever at least one *t*-alkoxy group is present in the molecule. The more that are present the greater is the resistance to hydrolysis.

Other Reactions of Interest.--Whitmore (9) has reported several reactions of silanes that are interesting.



(11)

Reaction 11 reminds one of neopentylchloride except that reagents which will cause neopentylchloride to rearrange do not promote this rearrangement and neopentylchloride is not changed by the small amount of $AlCl_3$ required here.



(12)

Reaction 12 is also given by neopentyl bromide.

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Reported by P. H. Aldrich
January 23, 1948

THE REDUCTION OF KETONES BY PRIMARY ALCOHOLS IN THE PRESENCE OF ALKALI

Aromatic Ketones.--In 1877 Zagoumenny (1) reduced benzophenone to benzhydrol by heating with alcoholic potassium hydroxide.

$$C_6H_5COC_6H_5 \xrightarrow{160^\circ} C_6H_5CHOHC_6H_5$$

A study of various substituted benzophenones indicated that the nature and position of the substituent groups influence the ease of reduction of the ketone group. With CH_3- substituent, the ease of reduction decreases in the order: p- > m- > o-. The halogen-substituted benzophenones are easily reduced. Sometimes the halogen atom is replaced by hydrogen in the following order: I > Br > Cl, and o- > p- > m-. The presence of an amino group inhibits the reaction, and no reaction takes place when the amino group is in the o- or p-position. Introduction of Cl or Br atoms into the benzene nucleus removes the hindrance in some cases. Both hydroxy and ethoxy groups are found to exercise hindering influence, the $OH > OC_2H_5$ (2).

p-$CH_3C_6H_4COC_6H_5$ → p-$CH_3C_6H_4CHOHC_6H_5$

2,4,6-$(CH_3)_3C_6H_2COC_6H_5$ → no reaction

α-$C_{10}H_7COC_6H_5$ → α-$C_{10}H_7CHOHC_6H_5$

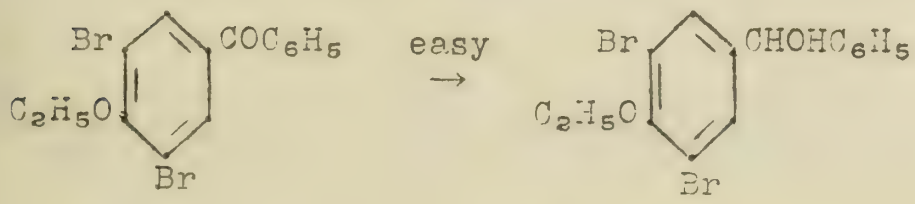
p-$ClC_6H_4COC_6H_4Cl$-p → p-$ClC_6H_4CHOHC_6H_4Cl$-p

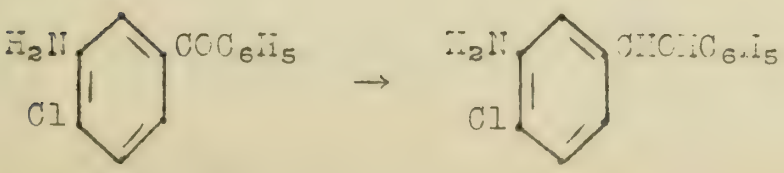
p-$HOC_6H_4COC_6H_4Cl$-p → no reaction

2,4,6-$Cl_3C_6H_2COC_6H_5$ → 2,4,6-$Cl_3C_6H_3$ + $C_6H_5CO_2H$

2,4,6-$Br_3C_6H_2COC_6H_5$ → p-$BrC_6H_4CHOHC_6H_5$

2- or 4-$IC_6H_4COC_6H_5$ → $C_6H_5CHOHC_6H_5$





Alcoholic potassium hydroxide also reduces anisyl-3-hexanone-4 to its carbinol (3).

$$CH_3CH_2CH(C_6H_4OCH_3\text{-}\underline{p})COCH_2CH_3 \xrightarrow{200\text{-}220^\circ} CH_3CH_2CH(C_6H_4OCH_3\text{-}\underline{p})CHOHCH_2CH_3$$

By use of potassium benzyloxide in benzyl alcohol, some aromatic-aliphatic ketones can be reduced (4,5).

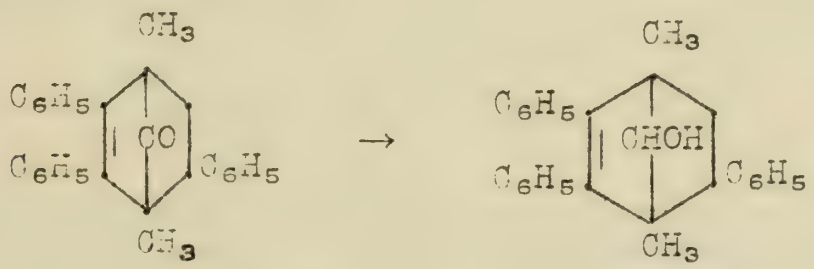
$$C_6H_5COCH_3 \rightarrow C_6H_5CHOHCH_2CH_2C_6H_5$$

$$\underline{p}\text{-}CH_3C_6H_4COCH_3 \rightarrow \underline{p}\text{-}CH_3C_6H_4CHOHCH_2CH_2C_6H_5$$

$$\beta\text{-}C_{10}H_7COCH_3 \rightarrow \beta\text{-}C_{10}H_7CHOHCH_2CH_2C_6H_5$$

$$\underline{p}\text{-}(CH_3)_2NC_6H_4COC_6H_4N(CH_3)_2\text{-}\underline{p} \rightarrow \underline{p}\text{-}(CH_3)_2NC_6H_4CHOHC_6H_4N(CH_3)_2\text{-}\underline{p}$$

Certain aliphatic bridged-ring ketones can be reduced smoothly to the carbinol by sodium or sodium ethoxide in dry ethanol (6).



Aliphatic Ketones.--The reduction of methylheptenone was recorded by Tiemann (7) and confirmed by Doeuvre (8), using alcoholic potassium hydroxide.

$$(CH_3)_2C{=}CH(CH_2)_2COCH_3 \rightarrow (CH_3)_2{=}CHCH_2CH_2CHCHCH_3$$

Schict (9) prepared some alcohols of high molecular weight by reduction of higher aliphatic ketones with aqueous alkali hydroxides and primary alcohols. Thus:

$$C_{17}H_{35}COC_{17}H_{35} \xrightarrow{200\text{-}300^\circ} C_{17}H_{35}CHOHC_{17}H_{35}$$

In order to establish the generality of the reaction, Hargreaves and Owen (10) performed the following experiments.

Diisopropyl ketone was treated with equimolecular quantities of methanol, ethanol or propanol in the presence of a concentrated aqueous solution of either sodium or potassium hydroxide, preferably the former, at 240° in a rocking autoclave. Hydrogen was liberated, and with one exception (methanol with KOH), reduction to diisopropyl carbinol occurred in all experiments. Formic acid could not be isolated from the experiment in which methanol was used, but acetic and propionic acid were obtained when ethanol and propanol, respectively, were the reducing agents, and the yield of carbinol was then ca. 55%. The same experiment was repeated using methyl n-butyl ketone and ethanol, n-propyl n-butyl ketone and n-butanol, methyl n-hexyl ketone and n-butanol. In all cases, the carbinols were obtained and a molecule of acid. Also, considerable amounts of high-boiling materials resulted from condensation of the alcohols under the vigorous conditions employed (11).

$$C_mH_{2m+1}OH + C_nH_{2n+1}ONa \rightarrow C_{m+n}H_{2(m+n)+1}OH + NaOH$$

(m and n may be equal) condenses further

Mechanism.--It is well known that primary alcohols when heated with aqueous alkali give the corresponding acid with liberation of two moles of hydrogen (12,13).

$$RCH_2OH \rightarrow RCO_2H + 2H_2$$

It is unlikely that this reaction is directly concerned in the reduction of ketones, since diisopropyl ketone was not reduced when heated with hydrogen and aqueous sodium hydroxide under the appropriate conditions.

In the study of the reduction of aldehydes by benzyl alcohol and potassium benzyloxide, a process analogous to that under discussion, the reduction was interpreted as occurring through an exchange of functions (4,5).

$$RCHO + C_6H_5CH_2OH \rightarrow RCH_2OH + C_6H_5CHO$$

$$2\ C_6H_5CHO + KOH \rightarrow C_6H_5CH_2OH + C_6H_5CO_2K$$

$$C_6H_5CHO + KOH \rightarrow C_6H_5CO_2K + H_2$$

Likewise, Hargreaves and Owen explained that the reduction of ketone is of the Meerwein-Ponndorf-Verley type (14) and may be represented as:

$$RCH_2OH + R'COR'' \rightleftarrows RCHO + R'CHOHR''$$

The equilibrium will not be maintained due to further conversion of the aldehyde to acid with liberation of hydrogen. It might appear that, in the case of a simple aliphatic aldehyde, condensation to an aldol or resin would supervene. It has been established that the introduction of acetaldehyde vapor into a mixture of sodium and potassium hydroxides at 250° results in a 90% yield of acetic acid, with the liberation of hydrogen (15). Therefore, the overall reaction is:

$$RCH_2OH + R'COR'' \rightarrow RCO_2H + R'CHOHR'' + H_2$$

Under the experimental conditions, secondary reactions occur, as the direct dehydrogenation of the primary alcohol to its acid and hydrogen, and the formation of high-boiling by-products.

<u>Scission of Ricinoleic Acid and α,β-Ethylenic Carbinols</u>.-- Ricinoleic acid in the presence of alkali undergoes scission to ketone and hydroxy acid at ca. 200°, while the carbinol and sebacic acid are the main products at temperatures above 240° (16,17,18,19).

$$\underset{\mathrm{I}}{CH_3(CH_2)_5CHOHCH_2CH{=}CH(CH_2)_7CO_2H}$$

$$\xrightarrow{\text{alkali ca. } 200^\circ} \underset{\mathrm{II}}{CH_3(CH_2)_5COCH_3} + \underset{\mathrm{III}}{CH_2OH(CH_2)_8CO_2H}$$

$$\xrightarrow{\text{alkali ca. } 240^\circ} \underset{\mathrm{IV}}{CH_3(CH_2)_5CHOHCH_3} + \underset{\mathrm{V}}{HO_2C(CH_2)_8CO_2H} + H_2$$

It has been recognized for some time that the ethylenic linkage in ricinoleic acid is capable of migration towards the hydroxyl group (20, 21). So the mechanism for the alkaline scission of ricinoleic acid involves a preliminary isomerization of the ethylenic linkage from the β,γ- to the α,β-position, and is represented by the scheme below (22):

$$CH_3(CH_2)_5CHOHCH{=}CH(CH_2)_8CO_2H$$

$$\downarrow$$

$$CH_3(CH_2)_5CHOHCH{=} + {=}CH(CH_2)_8CO_2H$$

$$\downarrow \qquad\qquad \downarrow + H_2O$$

$$\underset{\mathrm{II}}{CH_3(CH_2)_5COCH_3} + \underset{\mathrm{III}}{CH_2OH(CH_2)CO_2H}$$

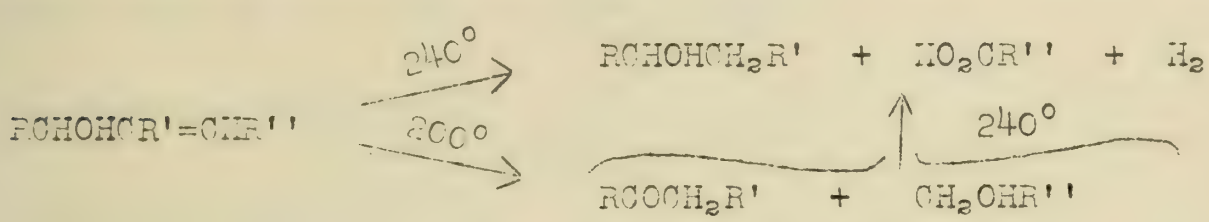
$$\downarrow\uparrow$$

$$CH_3(CH_2)_5CHOHCH_3 + OHC(CH_2)_8CO_2H$$

$$\mathrm{IV} \qquad\qquad \downarrow$$

$$\underset{\mathrm{V}}{HO_2C(CH_2)_8CO_2H} + H_2$$

If double-bond migration from the β,γ- to the α,β-position is the first step in the alkaline scission, it would be anticipated that α,β-ethylenic carbinols in general would also undergo fission with alkali; this is indeed the case, for it has been shown that such carbinols undergo both types of fission when heated with concentrated alkali to the appropriate temperatures.



Experiments have been performed with:

1. R = n-Bu, R' = H, R'' = Me
2. R = n-Bu, R' = Et, R'' = n-Pr

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Reported by L. C. Chou
January 23, 1948

SEMINAR TOPICS

II Semester 1947-48

THE POLYMERIZATION OF ACETYLENES

It has been recognized that, like most unsaturated compounds, acetylenes will undergo polymerization, but very few attempts have been made to determine the structures of the polymers or investigate the mechanism of the reaction except with acetylene itself or with propyne (1,2,3).

Acetylene undergoes thermal polymerization at 450°C or above to yield a complex mixture of aliphatic gases and a tarry liquid from which many aromatic compounds such as benzene and naphthalene can be isolated. A cork-like solid is also produced. This solid is obtained in better yield by polymerization of acetylene at 200-260° with a copper catalyst; the material is produced commercially under the name cuprene. It is believed to have an aromatic or partially aromatic structure (4). Alpha particles, cathode rays, excited mercury atoms, light and free radicals catalyze the polymerization of acetylene at lower temperatures; the polymers produced are in many instances quite different from those described above. There is no mention of peroxide catalysis in acetylene polymerization. Cyclo-octatetraene and other cyclopolyolefins are produced in excellent yield by the polymerization of acetylene under pressure in the presence of nickel cyanide (5). The formation of vinyl- and divinyl-acetylenes from acetylene in the presence of cuprous chloride is well known.

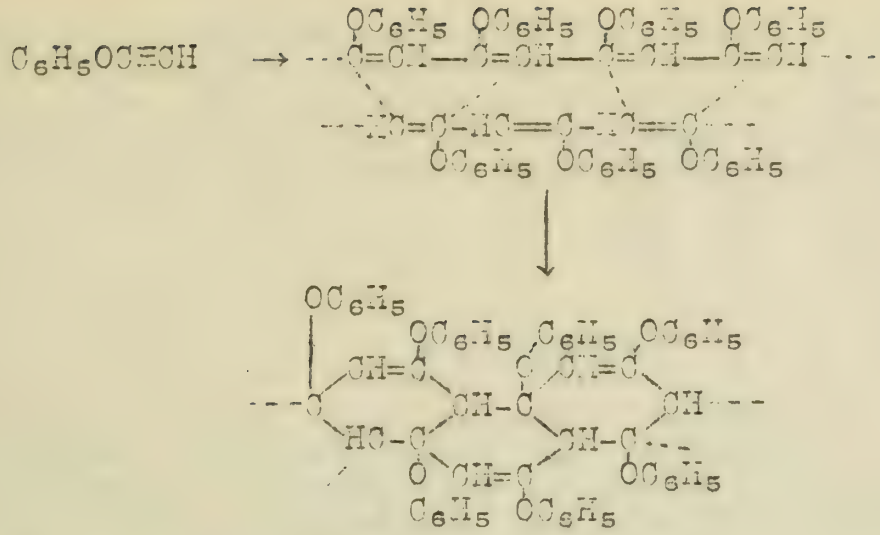
Propyne polymerizes at 500-650° to a non-aromatic liquid similar to that produced from allene (6). It was suggested that the polymerization is preceded by rearrangement to allene and that all 1-alkynes may rearrange similarly before polymerizing.

The polymerization of vinyl- and divinyl-acetylene is complex and occurs through the vinyl groups.

A survey of the literature indicates that those groups which are present in readily-polymerized vinyl compounds also activate the triple bond for polymerization.

Group	Acetylene	Ease of Polymerization	Ref.
$-C_6H_5$	$HC{\equiv}C-C_6H_5$	Readily at 230-240°	7, 8, 9
$-C{\equiv}N$	$HC{\equiv}C-C{\equiv}N$	Darkens at room temp.	10
$-CO_2R$	$HC{\equiv}C-CO_2R$	Uncertain	11, 12
$-CHO$	$HC{\equiv}C-CHO$	At room temp.	13
$-COR$	$HC{\equiv}C-COR$	Not affected by benzoyl peroxide at 100°	14
$-C{\equiv}CH$	$HC{\equiv}C-C{\equiv}CH$	At 0°C and above	15, 16
$-Cl$, $-Br$	$HC{\equiv}C-Cl$	Explosive decomposition	17-21
$-OCOCH_3$	$HC{\equiv}C-OCOCH_3$		
$-OR$	$HC{\equiv}C-OR$	At 0°C and above	

Phenoxyacetylene polymerizes spontaneously at room temperature to give a red, linear, conjugated polyene which undergoes cross-linking, possibly by a Diels-Alder reaction:



The first step in the reaction is readily followed by observing the rate of disappearance of monomer; this step is insensitive to the usual catalysts and inhibitors of vinyl polymerization, but is catalyzed by cadmium iodide. The linear polyene can be separated from cross-linked polymer chromatographically, or can be precipitated from samples polymerized for short periods only. Its conjugated nature is indicated by its ultraviolet absorption spectrum and by the brilliant colors produced with antimony trichloride (blue), strong mineral acids (blue) or bromine (violet).

The cross-linking reaction is accompanied by decreasing color and solubility. It appears to be catalyzed by acids. The sintering point of the polymers rises as the reaction proceeds, and the linear polymer will undergo thermosetting as expected. The molecular weights of the soluble polymers are only 4,000-8,000, and the polymers are relatively brittle. Half of the phenoxyl groups of the cross-linked material can be removed by heating under reduced pressure to 200°C, and the others are not removed even above 400°C. The polymerization does not involve attack of the phenyl groups however because the remaining phenoxyl groups are recovered as phenol when the polymer is fused with alkali.

Alkoxyacetylenes polymerize in a similar manner, but the reaction is slower; this is in contrast with the relative ease of polymerization of phenyl vinyl and alkyl vinyl ethers.

Preliminary studies on the polymerization of phenylacetylene show that it proceeds at a moderate speed at 140° and that the rate of disappearance of monomer is first order ($k = 2.0 \times 10^{-5}$ sec^{-1}).

Inhibitors for vinyl polymerization decrease the rate of the reaction, but are much less effective than with typical vinyl monomers. The polymers are of low molecular weight (500-1,000) and are yellow or orange. Their absorption throughout the ultraviolet region is high. Oxidation is difficult and no benzoic acid has been isolated.

Ozone is very incompletely absorbed and only high molecular

weight acids are isolated when the ozonide is decomposed with hydrogen peroxide. The polymer does not absorb hydrogen catalytically over platinum at room temperature. The infrared spectrum indicates the absence of the acetylenic linkage, but gives no information on the presence of a conjugated chain.

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Reported by Thomas L. Jacobs
February 20, 1948

ISOMORPHISM AND MISCIBILITY OF ORGANIC COMPOUNDS

It is now recognized that isomorphism in the full sense of the word does not exist, but that only approaches to this concept can occur (1). Since there are several criteria for isomorphic relations, such as miscibility, crystal-geometric similarity, seeding effects, physiological action, etc., the word isomorphism should be used only in connection with a word denoting the specific criterion employed. In this seminar, the ability of certain organic compounds to form mixed crystals will be discussed.

While several empirical rules concerning the miscibility of organic substances were developed in earlier years (2), no generalizations capable of furnishing a useful basis for further work existed until increasing knowledge of atomic or molecular structure made it possible to correlate the experimental results. Especially useful were the concepts of pseudoatoms and isosteres and their systematic arrangement by Grimm (3). Pseudoatoms are groups of atoms which in their properties resemble a chemical element (for example, NH_4^+ is a pseudo-alkali metal ion). This is assumed to depend on a shell consisting of equal numbers of electrons which surrounds the group of atoms. The term isostere, originally applied only to molecules containing the same number of atoms and electrons (for example, N_2 and CO), now is applied to molecules in which one atom or pseudoatom has been substituted by another containing the same number of electrons in the exterior shell.

A number of binary systems forming mixed crystals according to Grimm's hydride displacement law has been cited by Neuhaus in his excellent review (4). Some simple examples are the systems 1,4-dibromobenzene-p-bromotoluene, trichloroacetamide-tribromoacetamide, ethylene dibromide-succinonitrile.

Early application of these principles to the synthesis and investigation of physiologically active compounds was primarily due to H. Erlenmeyer (8) who more recently has been interested in comparison of benzene-thiazole analogs. An excellent example of two compounds which manifest both mixed crystal formation and similar pharmacological action is the system dimethylaminoantipyrene-isopropylantipyrene.

In addition to the rather specific exchanges which favor mixed crystal formation, there appear to be types of isomorphism depending on the general type of the crystalline building block. This is true in the n-paraffin series, for example, where it has been shown that in the region of C_{10}-C_{30}, members of a series differing by as much as three carbon atoms (9) or perhaps more (10) may form mixed crystals. Similarly, molecules of generally spherical form seem to have a surprising tendency to form mixed crystals (for example, camphor-tricyclene) (11). Many molecules of apparently planar form also form mixed crystals (4). A further variant is the isomorphism due to formation of dimers by one or both of the components, as in the system naphthalene-β-naphthol (12).

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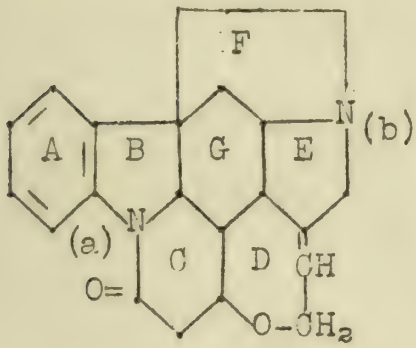
Reported by Werner Herz
February 20, 1948

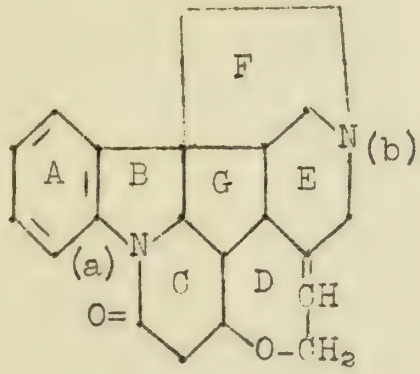
THE STRUCTURE OF STRYCHNINE

In 1939 Robinson (1) proposed a structure (I) for strychnine which explained most of the properties of the alkaloid known at that time. More recent work has led to several revisions in the structure.



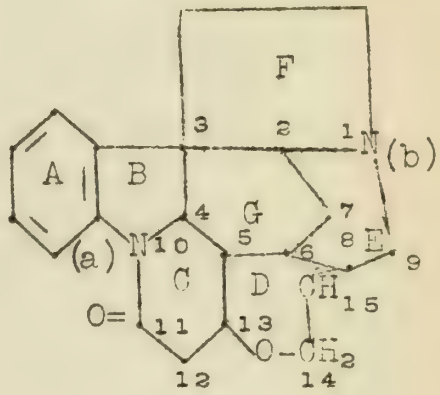
I

Robinson (1939)



II

Prelog (1945)



III

Robinson (1946)

Objections to Structure (I).--Prelog and Szpilfogel (2,3) in 1945 cited the following objections to structure (I).

1. The presence of β-collidine (4-methyl-3-ethylpyridine) in the alkaline degradation products of strychnine indicates that ring E is a β,γ-substituted piperidine rather than a pyrrolidine as postulated by Leuchs (4).

2. Degradation studies on ring E showed that it can undergo contraction which would be more probable for a 6-membered ring.

They suggested that these and other properties of strychnine are better explained by structure (II).

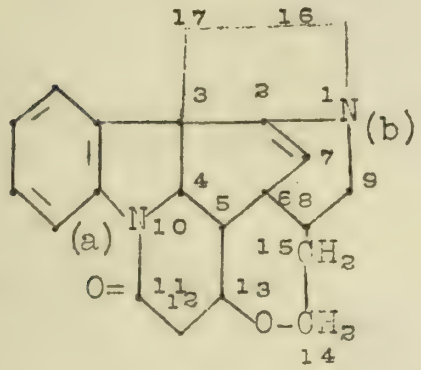
Objections to Structure (II).--According to Robinson (5) structure (II) is untenable for the following reasons.

1. Pseudostrychnine (hydroxystrychnine) is known to have a tert.-hydroxyl group on a carbon adjacent to N(b); $-\overset{>}{C}(OH)-N\overset{<}{}$(b). Structure (II) does not permit such a grouping.

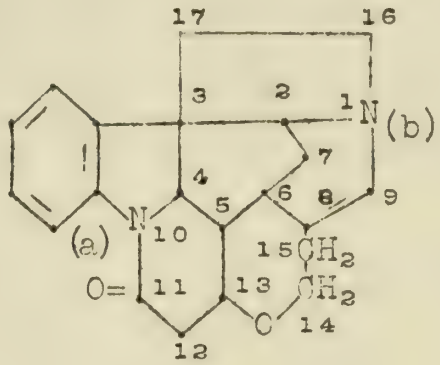
2. If it is assumed that ring E is 6-membered, then structure (III) should be considered since it provides for the structure of pseudostrychnine, and also explains more readily the presence of carbazole in the alkaline degradation of strychnine.

Structure of the Neo-bases.--Strychnine and a number of its derivatives can be converted to neostrychnine, an isomer differing only in the position of the double bond. The neostrychnine molecule was shown by Leuchs (7) to have a vinyl amine structure,

-C=C-N<(b), in contrast to strychnine where the double bond is in the allyl position to N(b). Robinson (8,9) later confirmed this, and suggested structure (IV) for neostrychnine. The other possible

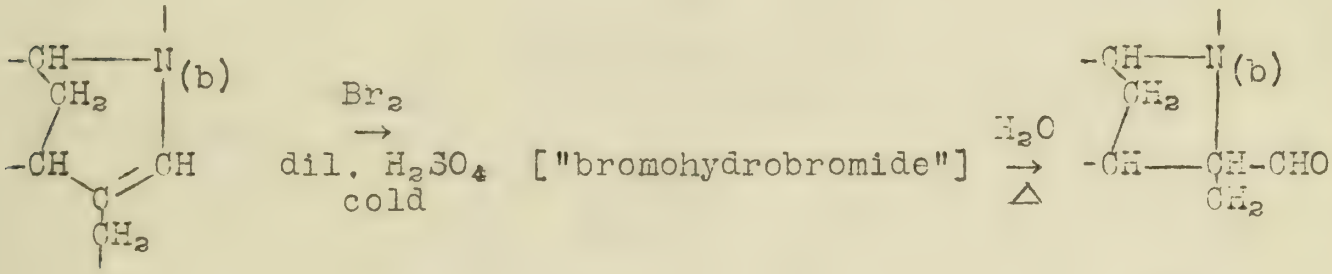


IV



V

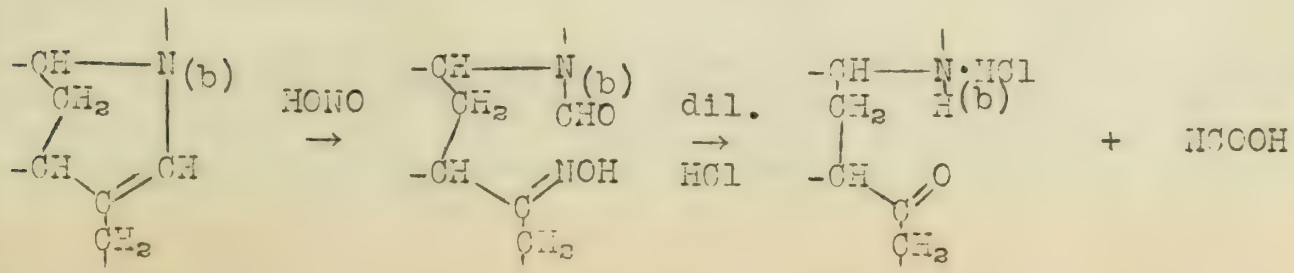
position of the double bond, shown in formula (V), was held untenable because oxidation should produce a formamide, and this reaction was not observed. Recently Robinson (10,11) reinvestigated the properties of neostrychnine, and proved that structure (V) is the correct one. Neostrychnine undergoes an oxidative rearrangement as shown in the partial formula below.



Oxodihydro<u>allo</u>strychnine

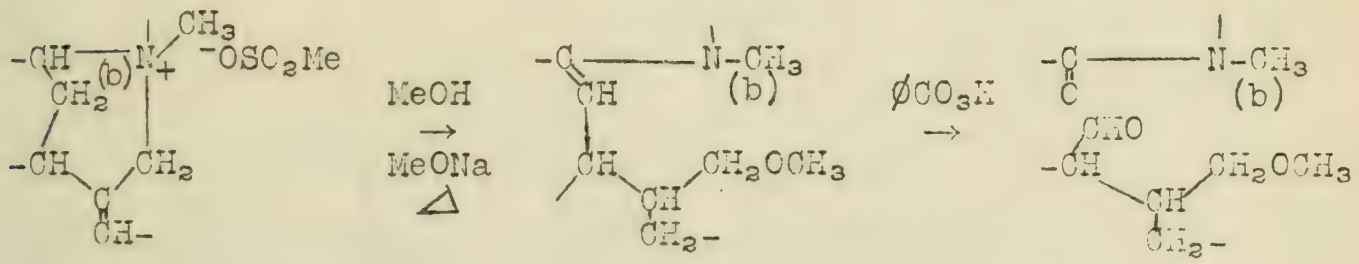
The presence of the aldehyde group in (VI) was well established.

Additional evidence for the location of the double bond at C_8C_9 was found in the following transformations.



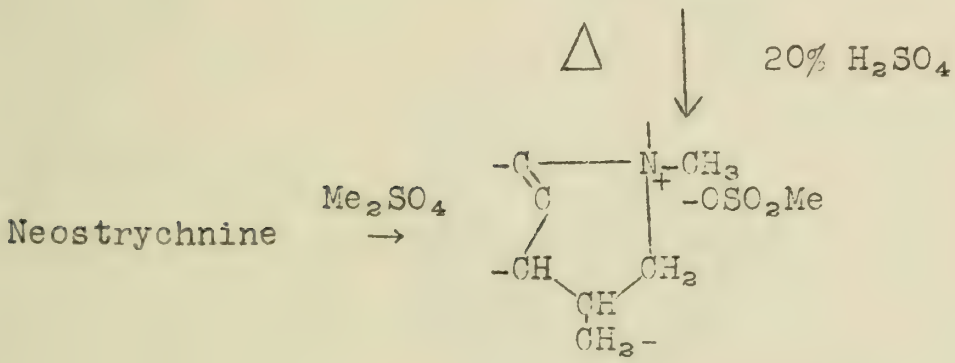
Compounds (VII) and (VIII) were isolated and identified as a ketoxime-formamide and a secondary basic ketone, respectively.

Structure of Methoxymethylchanodihydrostrychnone.--A series of reactions characteristic of derivatives of both the strychnine and neostrychnine bases has not been explained satisfactorily. An example is the transformation of strychnine methosulfate (IX) to methoxymethylchanodihydrostrychnone. Robinson first postulated this change on the basis of structure (IV) for neostrychnine.



IX X XII

Methoxymethyldihydroneostrychnine Methoxymethylchanodihydrostrychnone

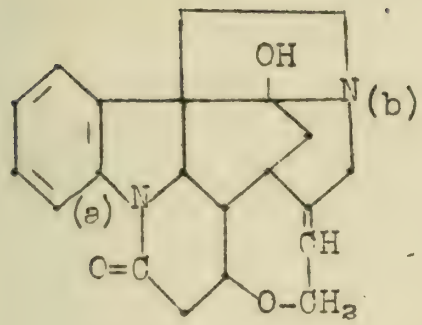


XI

Neostrychninemethosulfate

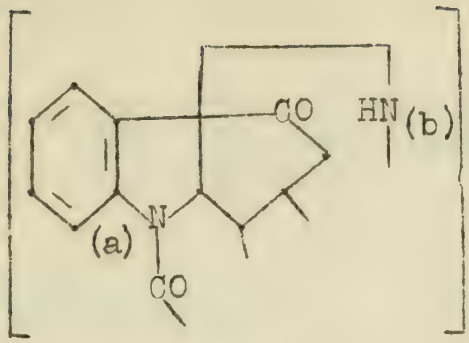
The compound (XII) was not an aldehyde, however, but a keto-amide. One proof of the presence of a keto group was the replacement of the carbonyl group in (XII) by a methylene group. These reactions further invalidate structure (IV) for neostrychnine, and whether structure (V) for neostrychnine will help in their interpretation remains to be seen.

Structure of Strychnone.--Pseudostrychnine (2-hydroxystrychnine) (XII) was oxidized by Leuchs (12) with acidic hydrogen peroxi to strychnone (XVI) which proved to be a lactam (at N(b)). Woodward (6) suggests that the reaction proceeds as follows.



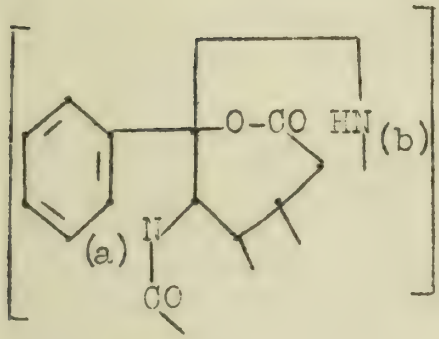
XII

→



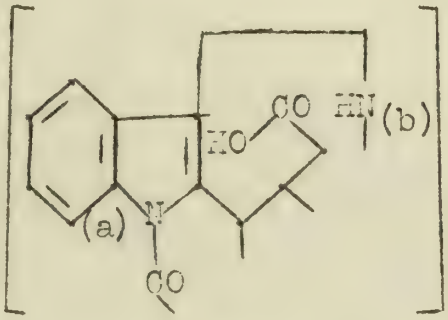
XIII

→



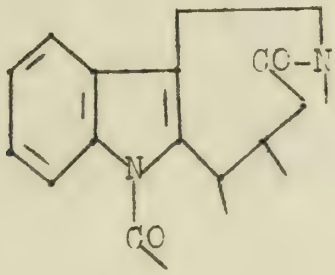
XIV

→



XV

→



XVI

Woodward found that the ultraviolet absorption spectrum of strychnone is similar to that of model N-acylindoles and quite different from that of strychnine and other N-acyldihydroindoles, in agreement with structure (XVI). He also suggests that the "strychnone hydrate" of Leuchs (12), formed by the action of HCl and water, is actually the amino acid: $-HN_{(a)}$ HOOC-. Furthermore the methoxydihydrostrychnone obtained by treating strychnone hydrate with methanol HCl is simply the ester: $-HN_{(a)}$ CH_3OOC-. None of the above substances give the Otto reaction, characteristic of N-acyldihydroindoles.

Conclusion.--The strychnine molecule is best represented by structure (III), and that of the neo-bases by structure (V). The methoxylating fission reaction illustrated by formulas (VIII) →

(IX) and the oxidation of methoxymethyldihydroneostrychnine (IX) are not yet explained. The formation and structure of strychnone as postulated by Woodward may be helpful in further degradation studies.

Included in the bibliography are a number of review articles covering the field prior to 1939, and miscellaneous recent references not discussed in this seminar.

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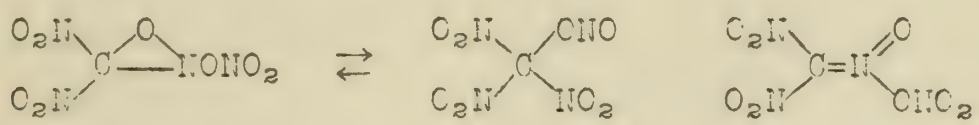
Reported by W. H. Jones
February 27, 1948

TETRANITROMETHANE
(TNM)

Preparation.--Tetranitromethane has been prepared from trinitromethane (1), diacetyl-orthonitric acid (2), various aromatic nitro compounds (3), acetic anhydride and nitrogen pentoxide (4), nitric acid and ethylene or acetylene (5), nitric acid and acetic anhydride (6), the latter method being adapted to Organic Syntheses recently (7). It involves treating pure nitric acid with acetic anhydride at 10°, and letting the mixture stand at room temperature for one week, getting 57-65% of product according to the reaction:

$$4HNO_3 + 4Ac_2O \rightarrow C(NO_2)_4 + CO_2 + 7AcOH$$

Properties.--Tetranitromethane is a colorless oil, melting at 13° and boiling at 126° (slight decomp.). If pure, it does not explode on rapid heating (1,7,8,9). Chemical reactions indicated to early workers that one or two nitro groups were different from the others and led to the equilibrium (10) and "nitrone" (11) structures shown:



However, measurements of dipole moment (12), Raman effect (13) and electron diffraction (14) have provided convincing proof that the symmetrical formula is correct.

TNM may be reduced to methylamine (15), guanidine (16), nitromethane (17) or trinitromethane by suitable reagents. Its reduction to nitroform by sodium ethoxide is dangerous (18), and it is recommended that potassium ferrocyanide be used (19), since it gives safe, rapid and quantitative reduction at 25°. Tetranitromethane reacts with aqueous KOH according to two competing reactions:

Dilute or
Conc. KOH - $C(NO_2)_4 + 2KOH \rightarrow KNO_3 + KC(NO_2)_3 + H_2O$

Dilute KOH - $3C(NO_2)_4 + 6KOH \rightarrow 4KNO_2 + K_2CO_3 + 3H_2O$

The first reaction increases in predominance from 66% in 0.1 N KOH to 92% in 14 N KOH (20). In acid medium HNO_2 is liberated.

Color Reactions.--Admixture of tetranitromethane with a compound containing an olefinic double bond results in the formation of a color which may vary from light yellow to deep brownish-red or even black. The reaction is not specific for double bonds,

however, colors being produced by sulfides, iodides, amines, phosphines and cyclic ethers. Moreover, it may be seen from the table that certain unsaturated compounds give a negative test. This fact has been used to locate double bonds in unsaturated acids (25).

COMPOUND	COLOR	REF.
paraffins	NC	22
cycloparaffins	NC	22,23
n-olefins	Y	21,22,26
dialkylethylenes	Y	26
trialkylethylenes	Y	26,27
tetraalkylethylenes	G,R	26
unconj. dienes	Y	26
allenes	Y	26
acetylenes	Y	26
conjugated dienes	O,R	22,26
cyclohexene	Y	26
pinene	O	22
camphene	R	22
menthene	R	22
alkylbenzenes	Y	21,22,27
diphenyl	Y	21,22
dibenzyl	Y	21
naphthalene	G,R	21,22
fluorene	O	21
stilbene	O	21
acenaphthene	R	21,22
anthracene	R-B	21,22
phenanthrene	O	21
retene	O	21,22
chrysene	R	22
pyrene	R	22
alkyl chlorides	NC	27
ethyl bromide	NC	27
ethyl iodide	Y	27
chloroalkenes	NC	27
chlorobenzene	Y	27
alcohols	NC	22
glycols, etc.	NC	22
α,β-unsatd. alcs.	Y,G	22
oleyl alcohol	O	22
cholesterol	Y	22
phenol, naphthols	R	22
catechol	R	22
resorcinol	R	22
hydroquinone	B	22
pyrogallol	R	22
safrole	Y	27
isosafrole	O	27
ethers	NC	22
anethole	Y	21

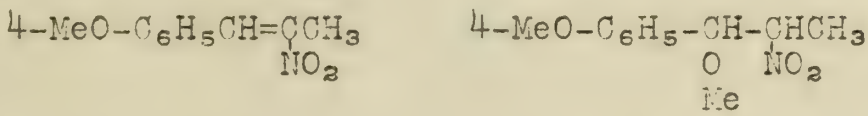
COMPOUND	COLOR	REF.
anisole	R	22
pyran	Y	27
dioxane	Y	27
ketones	NC	22
α,β-unsatd. ketones	NC	22
citral	O	22
piperitone	Y	25
vanillin	Y	22
acetoacetic ester	Y	22
esters	NC	22
coumarin	Y	22
acids	NC	21,24,27
α,β-unsatd. acids	NC	21,22,25,27
oleic acid	Y	24
linoleic acid	Y	21
9,12-linoleic acid	G	24
9,11-linoleic acid	R	24
linolenic acid	O	24
eleostearic acid	R	24
benzoic acid	NC	22
nitro compounds	NC	22
amides	NC	27
diphenylurea	Y	22
trimethylamine	B	21
β-NH_2 crotonates	Y	27
Me piperidine	G	27
Me morpholine	G	27
1,4-Me_2 piperazine	B	27
N,N'-Me_2 putrescine	B	27
arylamines	Y	21
aniline	R	22
naphthylamines	R	22
anthranilic acid	R	22
pyridine	Y	22
quinoline	R	22
4-covalent 3 cpds.	NC	27
alkyl sulfides	Y	27
cyclic sulfides	Y-G	27
thioacetic acid	NC	27
thioacetamide	Y	27
thiourea	Y	27
Et_3P	Y,B	27
$(C_6H_5CH_2)_3P$	B	27

Color Code:

Y - yellow
G - golden
O - orange
R - red
B - brown
NC - no color

Nitroform and dibromodinitromethane generally react in the same way, but the colors are not so intense.

Nitration.--It was noted that with concentrated KOH, tetranitromethane yields only nitroform and KNO_3, and this has also been found true in very weak alkali if carried out in alcohol or acetone. Tertiary aromatic amines act as weak bases in this sense, reacting with TNM in the cold to yield their mononitro derivative (dimethyl-p-anisidine yields 92% of 2-nitro-4-methoxydimethylaniline as its nitroform complex, which is easily hydrolyzed). The reaction is unusual in that it permits the introduction of nitro groups in an acid-free medium. Non-basic compounds may sometimes be nitrated by adding pyridine to the mixture (p-cresol yields 60% of 2-nitro-4-methylphenol), and even the H atom on an olefinic carbon may be replaced when the double bond is conjugated with the benzene ring (anethole with TNM in pyridine gives structure I). Yields range from 30 to 80%. In the absence of pyridine and presence of alcohols, alkoxynitration takes place with saturation of the double bond, the yields being 70-80% (anethole with TNM in methanol gives structure II). It is claimed that hexanitroethane will also undergo these reactions (28).



I II

Cleavage of Tertiary Amines.--If the reaction between TNM and tertiary amines in the presence of pyridine is carried out in refluxing alcohol, rather than at 0°, the nitric acid set free exerts little or no nitrating power, but one of the alkyl groups of the N is split off as aldehyde and replaced by a nitroso group (40-96% yields) (29). It was also found that replacing the pyridine by acetic acid gave good yields and was the superior method for cleaving aliphatic tertiary amines (30). Thus, tributylamine with TNM in acetic acid and alcohol at 100° for 3 hours yields 92% of N-nitrosodibutylamine. Cleavage of tertiary amines by nitrous acid (31) is well known, as is cleavage by nitric acid in acetic acid (32).

Oxidation Reactions.--TNM oxidizes hydroquinone to quinone and dimethylaniline to crystal-violet (22); triphenylhydrazine has been oxidized by TNM to the blue-green compound (33):

It has been qualitatively observed that tetranitromethane causes elaidinization and polymerization of vegetable oils, and converts

elaidic acid into a mixture of azelaic acid, pelargonic acid, pelargonic aldehyde and 9,10-diketostearic acid. Similarly, stilbene, 2-butene and erucic acid gave the corresponding acids, aldehydes and diketo derivatives which would be expected (24). Such a reaction is probably not less useful or more dangerous than ozonization.

Hazards.--TNM is very poisonous, affecting the membranes of the eyes and nose at first, but capable of causing death (35,36, 37). Color tests with TNM occasionally result in explosive reaction if allowed to stand at room temperature, but may be remedied by dilution, cooling and use of small quantities (8). Serious accidents have occurred (38) and it is believed that mixtures of TNM with aromatic hydrocarbons form the most sensitive and destructive composition possible today (39,40,41).

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Reported by Wilson M. Whaley
February 27, 1948

ALPHA NITRO OLEFINS

Current interest in alpha nitro olefins ($R_2C{=}CRNO_2$) stems from the possibility of using them as intermediates in the commercial preparation of certain alpha nitro and amino compounds such as polymers, ethers, sulfides, sulfonic acids, alkyl and aryl cyanides, and certain nitro paraffins and 1:3-diamines. Most of the work reported has been with nitro olefins of low molecular weight, namely nitroethylene, 2-nitro-1-propene, 1-nitro-2-methylpropene, 2-nitro-2-butene, and beta nitro styrene.

Preparations.--Alpha nitro olefins are easily prepared from alpha nitro alcohols, esters, and secondary amine salts because of the activating influence of the alpha nitro group. The reactions can be summarized as follows:

$$R\overset{H}{\underset{NO_2}{C}}-CR_2X \rightarrow R-\underset{NO_2}{C}{=}CR_2 + HX \qquad (50\text{-}96\%)$$

where X stands for -OH, $-O\overset{O}{\overset{\|}{C}}CH_3$, $-O\overset{O}{\overset{\|}{C}}\emptyset$, or $-NR_2{\cdot}HCl$ and R stands for hydrogen or alkyl groups.

Alpha nitro alcohols are dehydrated by $NaHSO_3$, P_2O_5 (1), Ac_2O (2), and phthalic anhydride (3).

Alpha nitro esters (acetates or benzoates) yield alpha nitro olefins upon basic hydrolysis (usually employing $NaHCO_3$) (8,9), or pyrolysis (1,10). It should be pointed out, however, that olefins of low molecular weight cannot be prepared by basic hydrolysis of esters because they polymerize readily in basic medium.

Salts of alpha nitro secondary amines decompose upon heating (100-175°) to give alpha nitro olefins (11).

Reactions.

1. Polymerization.--Since alpha nitro olefins polymerize readily in basic medium, Blomquist (10) proposed using them as intermediates in the preparation of useful amine polymers.

$$\left(R\overset{R}{\underset{NO_2}{C}}-CH_2\right)_x \xrightarrow[\text{cat.}]{H} \left(R\overset{R}{\underset{NH_2}{C}}-CH_2\right)_x$$

However, catalytic hydrogenation was successful with only the 2-amino propene polymer. He suggested that the 1-hydrogen of the nitro ethylene polymer was protected by hydrogen bonding (R replaced by H in example above).

2. Normal Addition Reactions.--The addition reactions of alpha nitro olefins are analogous to those of α-β unsaturated esters, acids, aldehydes, ketones, and nitriles. These reactions can be summarized as follows:

$$R_2C{=}CHNO_2 + HY \xrightarrow[\text{catalyst}]{\text{basic}} R_2\underset{Y}{C}-CR_2NO_2$$

where Y stands for -OH, -OR, -SH, -SR, $-SO_3Na$, $-NH_2$, -NHR, -NHAr, -CN, $-CRR'NO_2$ and $\emptyset\underset{|}{C}HCN$.

a. H_2O, ROH (12), RSH, and H_2S (14) react readily in the presence of a basic catalyst (usually NaOMe) to give alcohols, ethers, sulfides, and mercaptans. The alcohols and mercaptans can react further to yield symmetrical ethers and sulfides. Oxidation of the nitro alkyl sulfides with hydrogen peroxide in acetic acid afforded the nitro alkyl sulfones. Yields in most cases are good (90%).

b. NH_3, and primary and secondary amines (15), interact with alpha nitro olefins giving 2-nitro alkyl amines. However, the products are in general extremely unstable. The N-2-nitro alkyl-arylamines are stable enough to be isolated and characterized through their salts.

c. HCN (4) and aryl methyl cyanides (5) react readily in the presence of a basic catalyst (KCN or potassium tertiary amyl oxide) to yield nitro cyanides. Buckley believes this reaction will make possible the preparation of a wide variety of hitherto inaccessible compounds.

$$O_2NCH{=}CH_2 + \underset{Ar}{C}H_2-CN \rightarrow NO_2CH_2CH_2\underset{Ar}{C}HCN$$

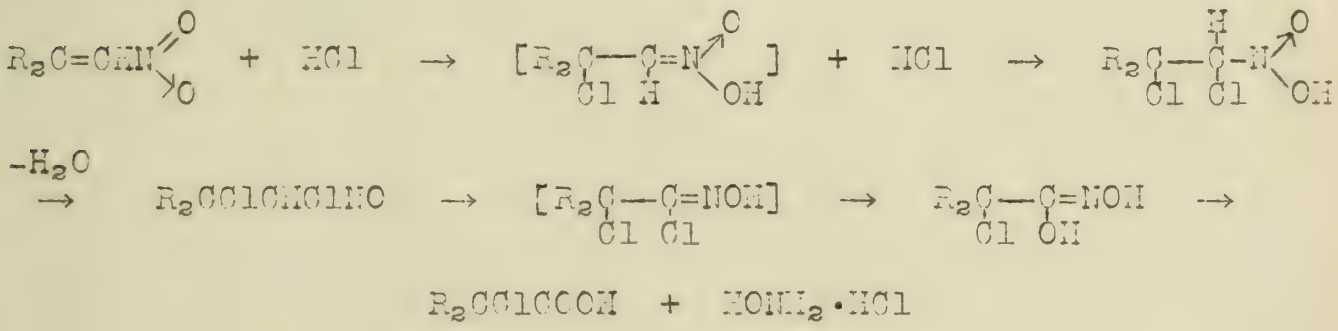
d. $NaHSO_3$ (16) reacts with alpha nitro olefins to give 2-nitro alkane sulfonates in good yield. In the absence of oxygen, sulfurous acid can be used in place of $NaHSO_3$.

e. Primary or secondary aliphatic nitro compounds (13) interact with alpha nitro olefins in the presence of NaOMe to yield 1:3-dinitro paraffins. The reaction is general, but the yields are variable, because of polymerization of the alpha nitro olefin.

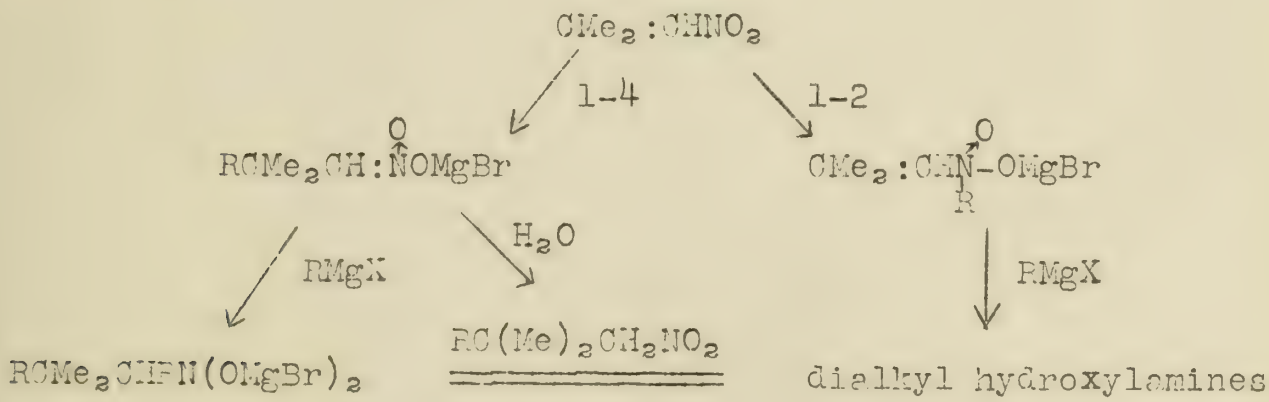
All the above compounds, with the exception of the nitro alkyl and aryl cyanides, have been reduced in good yields (R Ni and H) to the corresponding amine derivatives. When 1-nitro-2-cyanoalkanes were reduced catalytically (4), surprising results were obtained. Instead of getting the desired 1:3-diamino derivative, a low yield of the 3-amino amide was obtained. No

information was found concerning the reduction of aryl nitro cyanides.

3. Addition of HCl (17).--Alpha nitro olefins react with anhydrous hydrogen chloride in ether giving 1:2-dichloronitroso compounds which rearrange, if an alpha hydrogen is present, into 1:2 dichloro-oximes. These on hydrolysis with water afford hydroxylamine hydrochloride and an alpha hydroxy- or alpha chloro-carboxylic acid according to the extent of the reaction. Heath and Rose propose the following mechanism:



4. Addition of organo metallic halides (6,7).--A series of hitherto unknown or inaccessible nitro-paraffins has been prepared by 1:4 addition of alkyl or aryl magnesium halides or alkyl zinc halides to alpha nitro olefins. By carrying out the reaction below 10° and avoiding excess of organometallic halide, secondary reactions are almost completely suppressed. Yields of around 65% have been obtained. The low yield is due to the simultaneous occurrence of some 1:2 addition. Buckley proposed the following mechanism:



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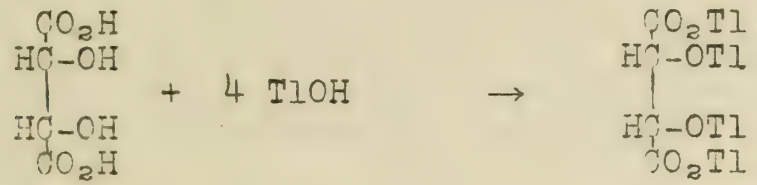
Reported by Nils K. Nelson
March 5, 1948

THE USE OF THALLIUM IN ORGANIC CHEMISTRY

Thallium organic compounds are prepared by the action of thallous hydroxide or thallous ethoxide on the labile hydrogen atoms of organic compounds (1).



$$\emptyset OH + TlOH \rightarrow \emptyset OTl$$

Gluconic Acid → Hexathallium gluconate (3)

Sorbitol → Hexathalium sorbitol (3)

Apparently all hydroxyl groups in straight chain compounds react, but substitution may be incomplete if a pyranose or furanose ring is present. For example, α-methyl glucoside gives a trithallium derivative in 85% yield (2). This incomplete thallation has been observed only in rings containing an oxygen atom. Thus inositol behaves normally, and yields hexathallium inositol. β-diketones such as ethyl acetoacetate will give the corresponding thallium salt. Thallium salts are crystalline, and can be obtained in pure form. The salts formed by β-diketones are readily soluble in organic solvents.

The alcoholic oxygen-thallium bond is hydrolyzed by water, and the thallium may then be determined by titration with standardized acid. The carboxylate thallium is determined by the precipitation of the metal as thallous iodide. Thus tetrathallium tartrate shows two thallium atoms by titration, and four by precipitation (3).

The preparation of thallous hydroxide and thallous ethoxide has been carried out as follows (4):

$$Tl_2O_3 + 2\ HCHO \rightarrow 2\ HCO_2Tl + H_2O$$

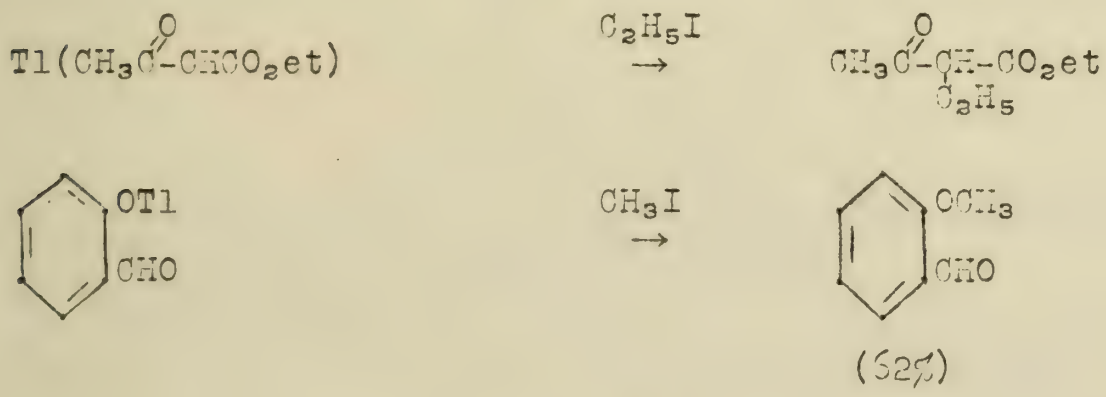
$$HCO_2Tl + NaOH \rightarrow TlOH + HCO_2Na$$
(80%)

$$TlOH + C_2H_5OH \rightarrow TlOC_2H_5$$
(absolute) (76%)

or: $$HCO_2Tl + Na \xrightarrow{\text{absolute } C_2H_5OH} TlOC_2H_5$$
(82%)

Thallium ethoxide can be stored if kept cool and away from light. It is completely miscible with benzene, n-hexane, and ether.

Alkylations with thallous organic compounds are carried out with alkyl iodides (2). They proceed smoothly if the thallous salt is soluble in the alkylating agent, or if the salt is amorphous in nature and presents a large surface. For example, thallous palmitate and stearate are soluble in methyl iodide, and in four hours give an almost quantitative yield of their methyl esters. Some other alkylation reactions:

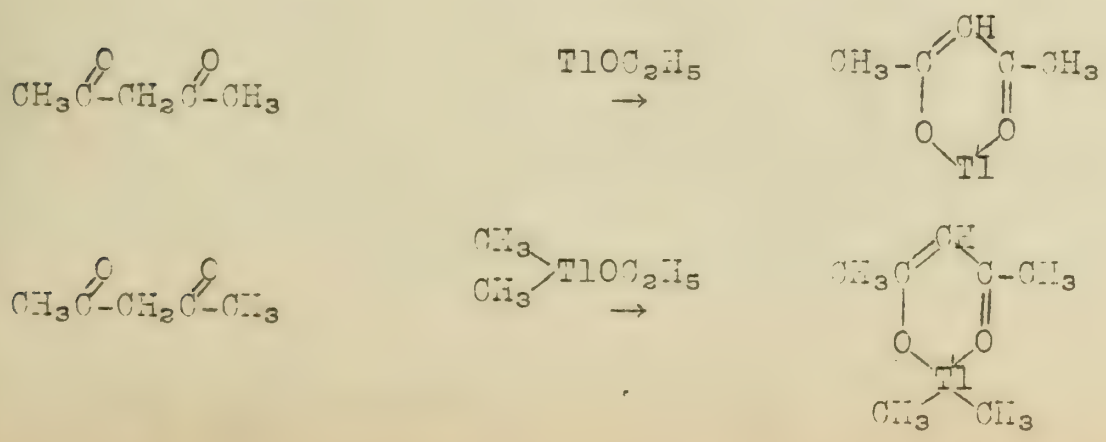


Thallous stearate $\xrightarrow{PrI}$ Propyl stearate (excellent yield)

Trithallium α-methyl glucoside $\xrightarrow{MeI}$ Trimethyl α-methyl glucoside (91%)

This method of alkylation is good for handling small amounts of material.

Menzies and Wiltshire performed a series of experiments on thallium chelation and association, using β-diketones (5a,b,c,d,e).



This alkylation is useful for the initial partial methylation in non-aqueous solvents of polysaccharides, where methyl sulfate and sodium hydroxide are ineffectual. Hirst and Jones have described the thallation and methylation of an arabo-pectic acid complex, and a number of vegetable gums (6a,b,c) (7a,b,c,d). Purves and Hudson methylated α-methyl, α-benzyl, and β-benzyl fructofuranoside by use of thallous ethoxide and methyl iodide, followed by silver oxide and methyl iodide. They also used thallous ethoxide to methylate the exposed hydroxy groups of cellulose in ether or benzene, thus avoiding swelling of the material and consequent exposure of more hydroxyl groups.

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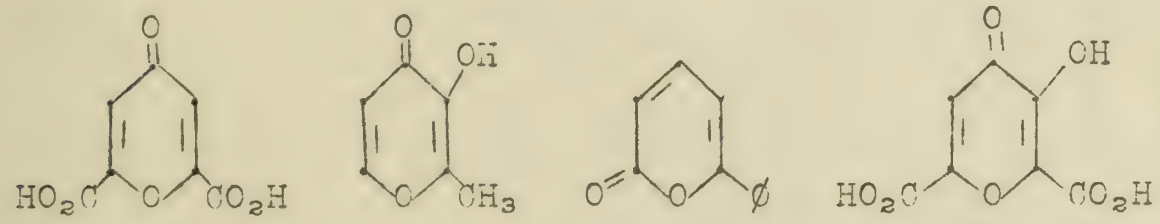
General Reference: Menzies, J. Chem. Soc., 1378 (1947).

Reported by M. Rothstein
March 5, 1948

REACTIONS OF MONOCYCLIC α- AND γ-PYRONES

The frequent occurrence of monocyclic pyrones in natural products led to early investigation of their preparation and reactions.

Compound	Source
chelidonic acid (A)	2% in lily of the valley leaves
maltol (B)	pine needles; larch bark
2-phenyl-α-pyrone (C)	coto bark
meconic acid (D)	opium alkaloid sources



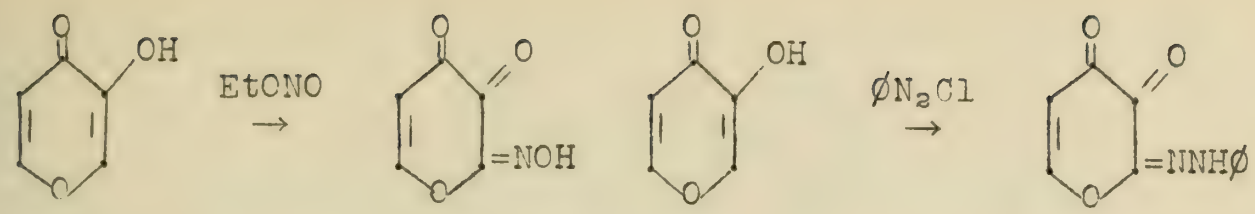
A B C D

1. Lactonic Structure.--The easy opening of the pyrone ring by alkalies and its reformation with acids, the failure to form an oxime and hydrazone, and the inability to undergo the reduction common to ketones demonstrate that the carbonyl group in the gamma position is, indeed, of the same type as is present in lactones, further stabilized by resonance of electrons. The γ-pyrone molecule must thus be regarded as a lactone with the carbonyl group and oxygen atom doubly connected by vinylogous systems. The enol-lactone structure in α-pyrones is immediately apparent.

2. Resonance.--Dipole moment measurements (1,2) indicate that resonance forms make a major contribution to the actual state of the molecule. Parachor measurements (3) and ultraviolet absorption data (4) show that ketone forms also contribute to a lesser extent.

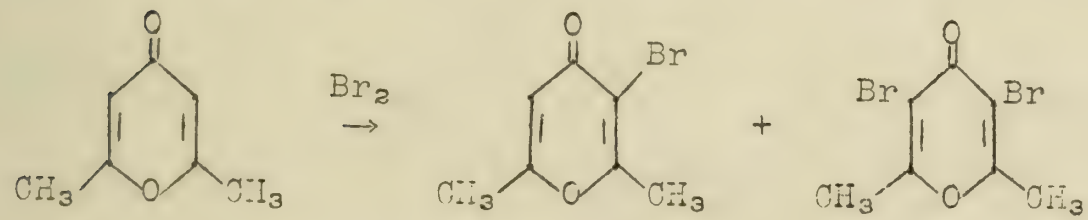
3. Unsaturation.--Halogens and halogen acids do not add; the Michael reaction fails; but the Diene synthesis occurs with α-pyrone derivatives (5).

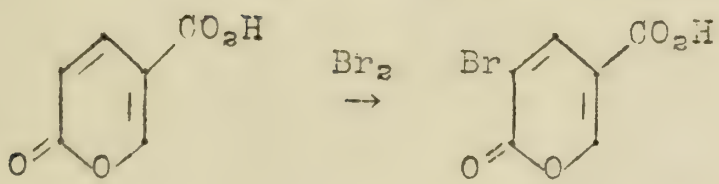
4. Tautomerism.--Enol and keto forms of hydroxy pyrones are known to exist. The $FeCl_3$ test is positive, and methyl ethers, benzoates, acetates, and urethanes are easily formed. Keto forms can be demonstrated as follows:



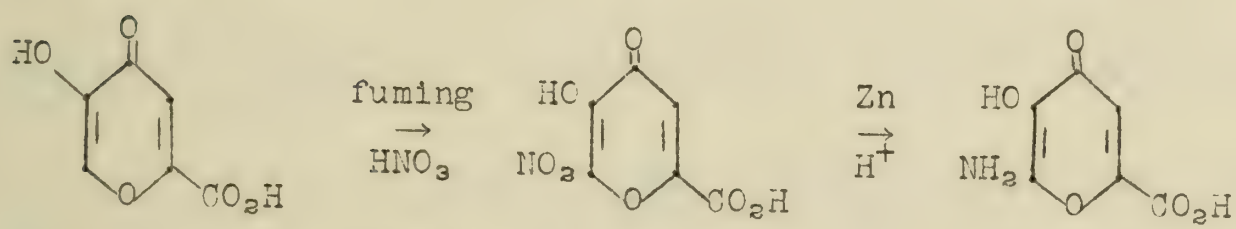
5. Aromaticity.--

a. Halogenation (substitution)

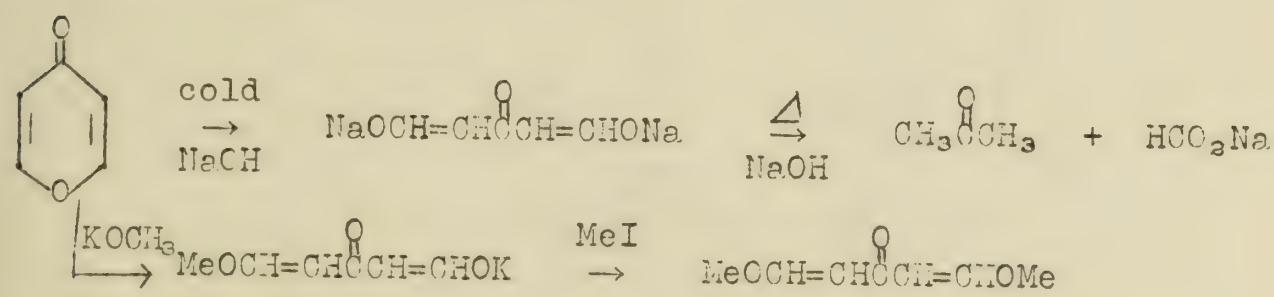




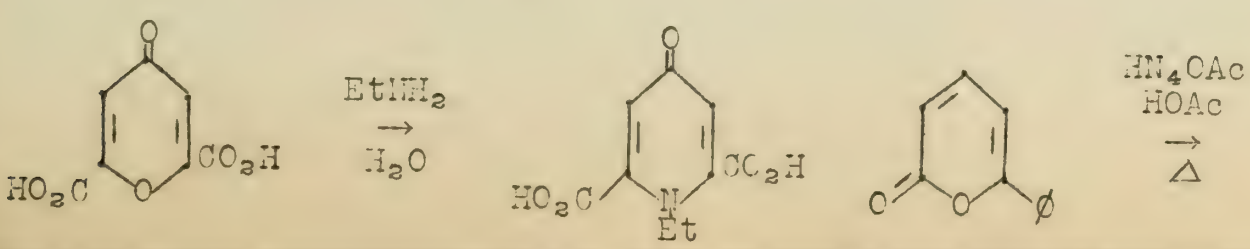
b. Nitration (difficult)

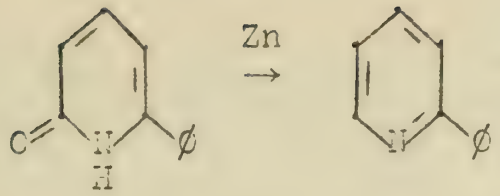


6. Basic Cleavage.-- γ-Pyrones are cleaved by bases much more predictably than are α-pyrones. The latter give complex mixtures of degradation products.

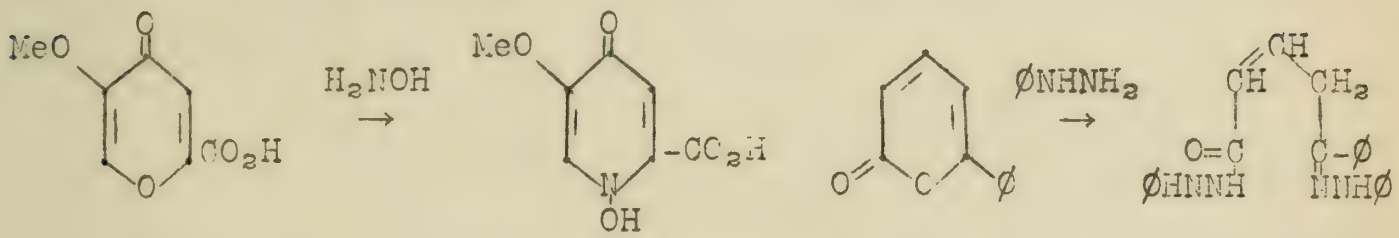


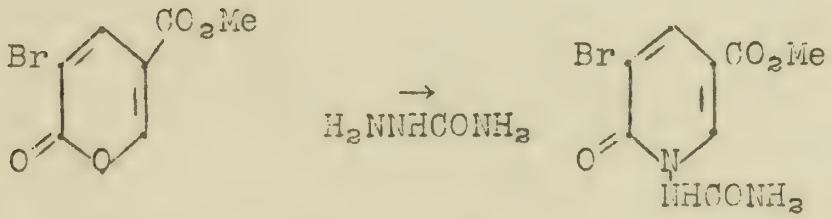
7. Ammonia and Primary Amines.--In general these lead to pyridones. Secondary and tertiary amines cleave the ring and recyclization cannot occur.





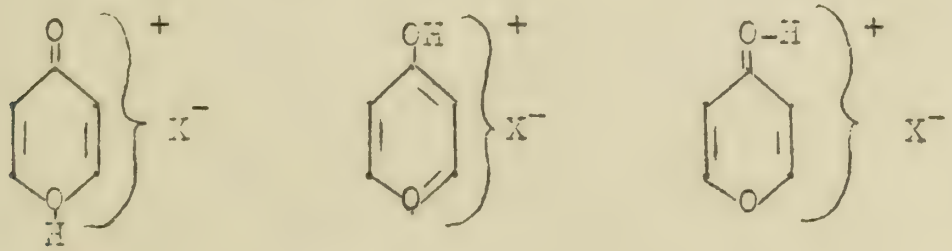
8. Carbonyl Functions.--These are largely absent. Reactions are anomalous and depend on both reagent and compound.





9. Reduction.--Catalytic reduction to tetrahydropyrones is frequently successful. $PdCl_2$, Raney Ni, and Pd on $BaSO_4$ are usually employed.

10. Pyroxonium Salts and Basic Strength.--The basicity of α- and γ-pyrones is due to one or both of the oxygen atoms, but only γ-pyrones are known to form pyroxonium salts upon the addition of organic or inorganic acids. The structure of these salts is still undetermined, although the ratio of acid to pyrone may be 1:1, 2:1, or even 3:2. Three structures have been proposed:



The basic strength of pyrones has been determined by conductimetric methods. 2,6-Dimethylpyrones are slightly stronger bases than urea, and tetramethyl pyrones are weaker than urea. α-Pyrones are least basic of all.

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Reported by T. E. Bockstahler
March 5, 1948

BENZOPOLYMETHYLENE COMPOUNDS

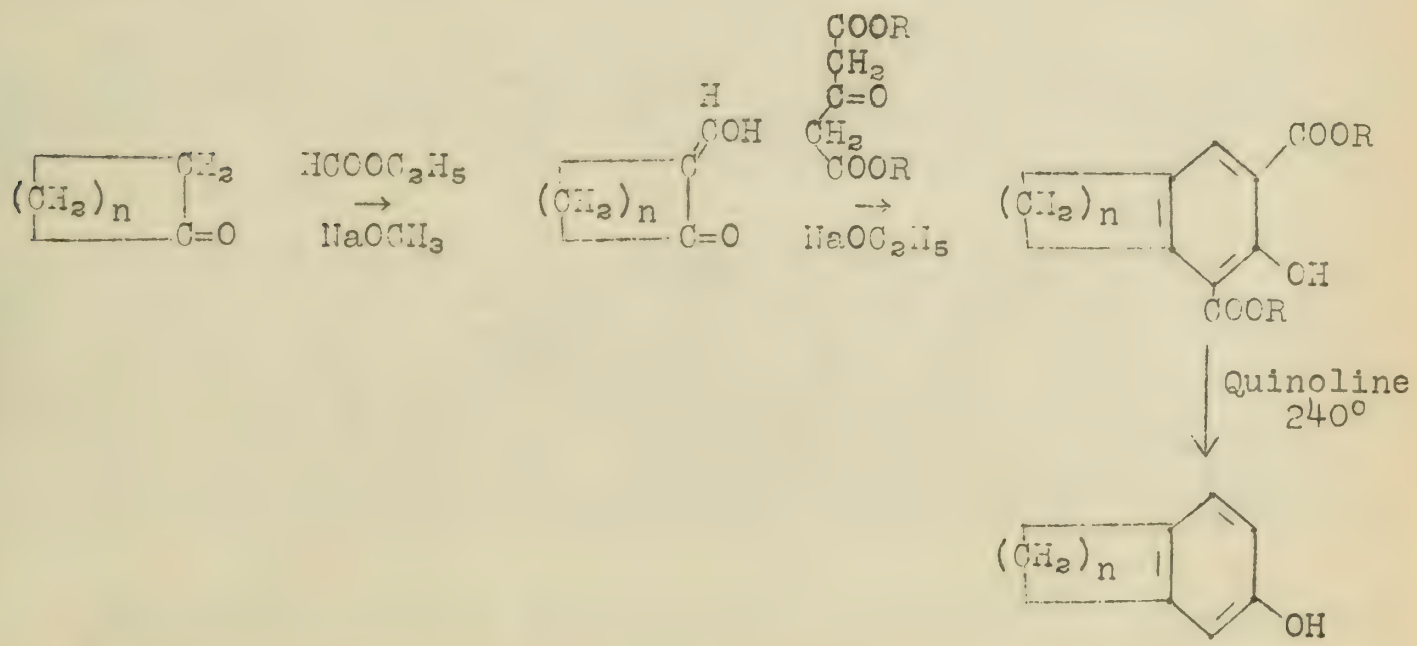
Historical.--As early as 1901 (1) aliphatic rings were combined with aromatic rings by the Friedel-Crafts reaction, and in 1928 Titley (2) synthesized some o-benzopolymethylene compounds by a Dieckmann reaction, but his attempts to extend the method to the meta and para compounds failed.

It was not until 1932 that a meta- and para-benzopolymethylene compound was synthesized (3) by heating the cerium salt of the corresponding dibasic acid. Evidence was presented at this time which indicated that a bridge of at least twelve members is necessary to span the 1,4 positions of the benzene nucleus.

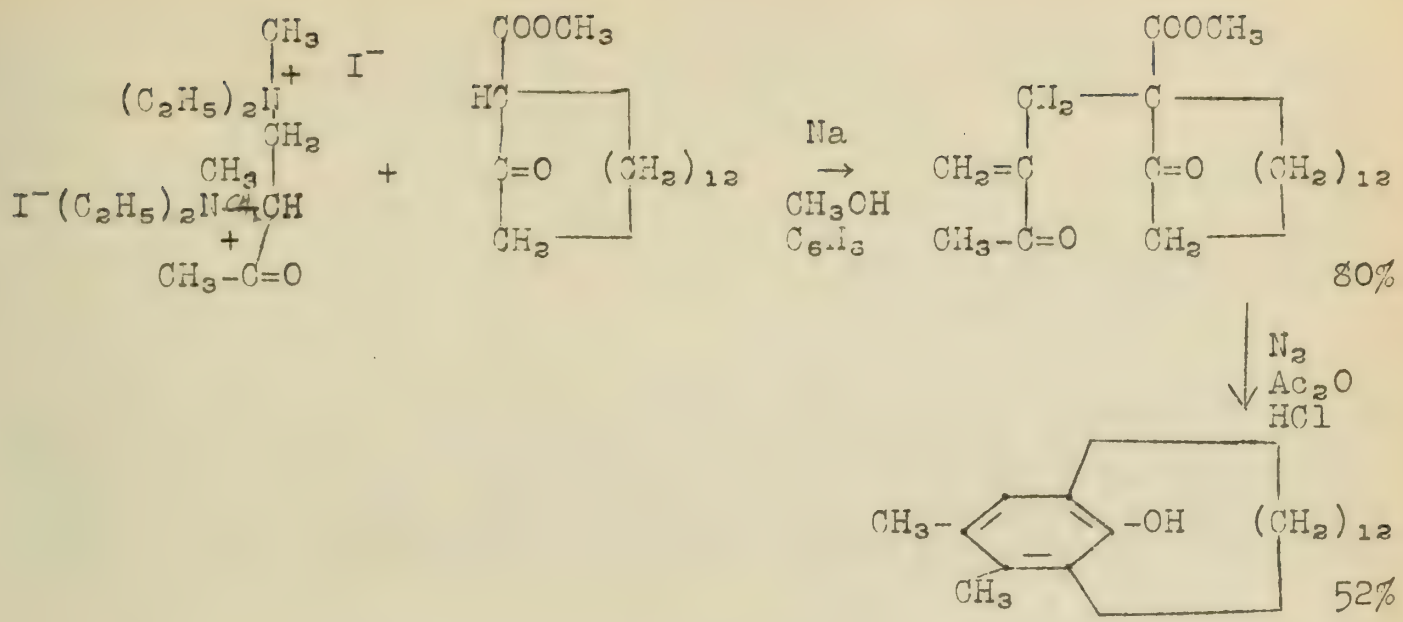
In 1933 Plant (4) stated that with models a m-benzoheptamethylene compound could be built which did not exhibit undue strain. Attempts to synthesize a seven-membered bridge in the laboratory, however, were unsuccessful.

Two years later Ziegler and Lüttringhaus (5,6) described the synthesis of the 1,3- and 1,4-phenylenepolymethylene ethers, and continued efforts along these lines enabled Lüttringhaus (7) to report the preparation of 1,3-phenyleneheptamethylene ether. This represents the smallest such bridge known up to the work of Prelog and Wiesner (8) in 1947.

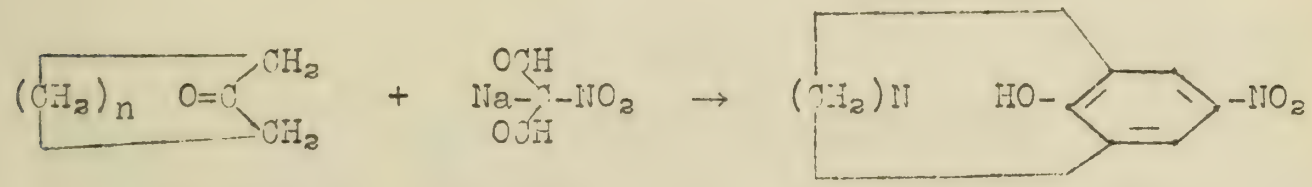
Preparation.--It is to be noted that all previous attempts to bridge the benzene ring involved a ring closure of the corresponding disubstituted benzene. Prelog reversed the order of approach, and synthesized the aromatic ring after the alicyclic one. To obtain the o-benzopolymethylene compounds (9), the following reactions were carried out:



The m-benzopolymethylene compound was synthesized as follows (10,11):



It was known that sodium nitromalonaldehyde (12) could be allowed to react with ketones to form p-nitrophenols (13,14,15,16). Accordingly, Prelog and Wiesner (8) applied cyclic ketones to the reaction, and obtained the 2,6-polymethylene-4-nitrophenols.

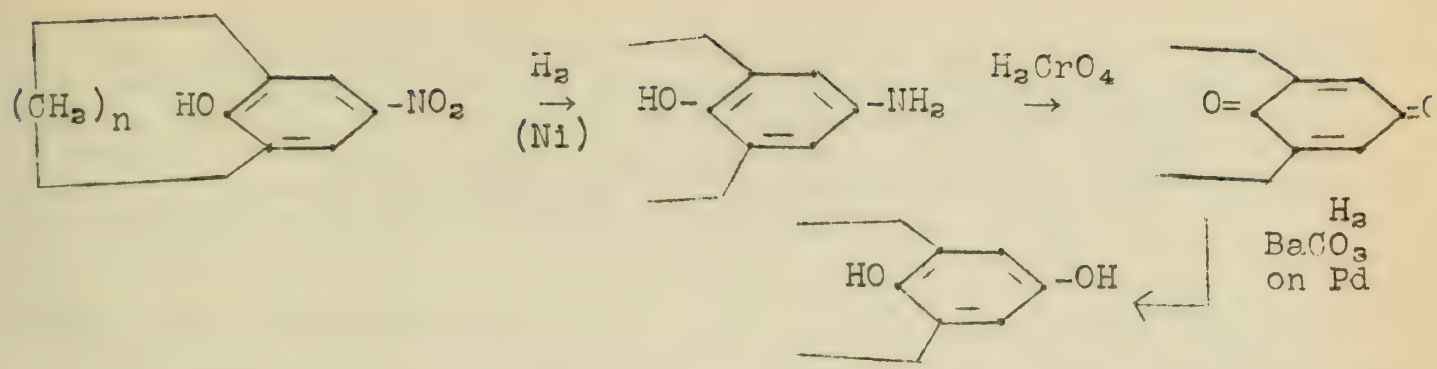


Compounds were synthesized with n = 5,6,7,9-15,17,18 and 27.

Preparation of Cyclic Ketones.--Since cyclic ketones containing nine through twelve carbons in the ring have not previously been obtained in good yield, it is of interest to consider briefly the method which Prelog, Frankiel, Kobelt and Barman (17) employed to achieve this end.

Sodium was dispersed in hot xylene, and the α,ω-dicarboxylic esters of suitable acids added with vigorous stirring to give 30-65% yields of the corresponding cyclic acyloins. One of the most interesting features of this cyclization is that it is unnecessary to work in high dilution, since the rate of reaction is sufficient to offset this consideration (18). The acyloins, along with the 1,2-diketones which are present as impurities, were then treated with zinc and hydrochloric acid in glacial acetic acid to give the desired cyclanones.

Properties.--Only a preliminary investigation of the properties of the 2,6-polymethylene-4-nitrophenols has been reported to date. They form the expected yellow water-soluble salts, and exhibit other p-nitrophenol reactions. Thus:



The absorption spectra resemble that of p-nitrophenol, but the maxima are shifted toward the visible range. As the size of the bridge decreases, the maximum is shifted more and more toward the longer wave lengths. The pentamethylene compound is an exception, however, with the maximum at a wave length even shorter than that for p-nitrophenol.

Stereoisomerism.--No mention is made of the possibility of stereoisomers of these compounds. Experiments with Fischer-Hirschfelder-Taylor models reveal that at least eleven methylene groups are needed to allow the polymethylene bridge to slip past the phenolic group. Thus, it should be possible to isolate stereoisomers of unsymmetrical compounds of this type.

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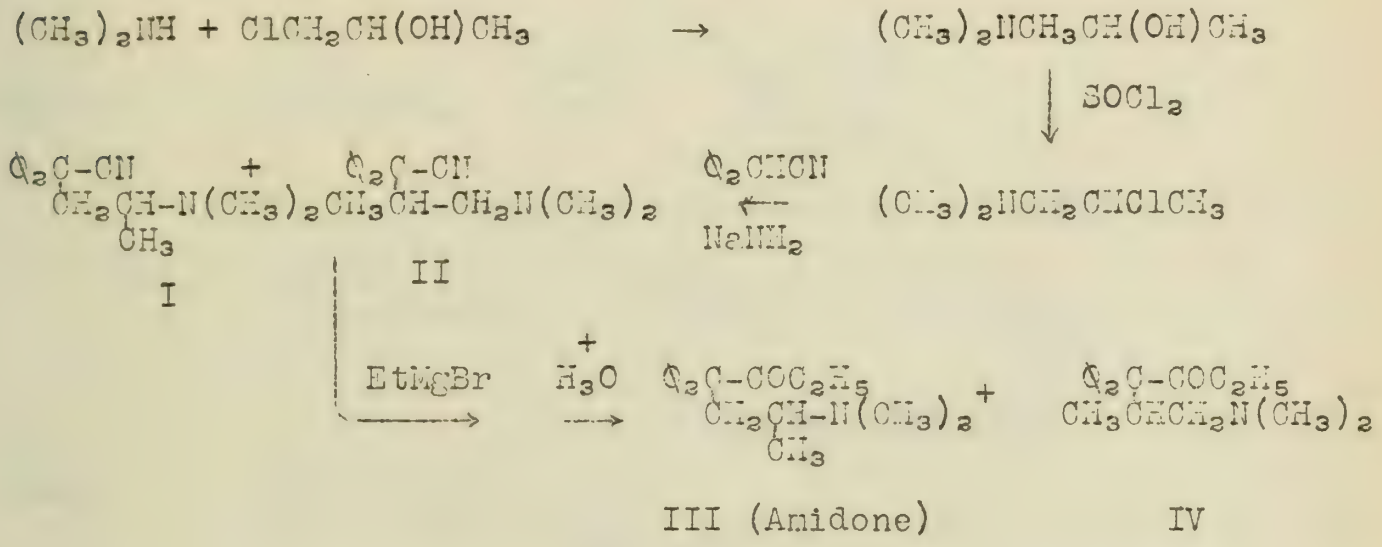
Reported by R. H. Mattson
March 5, 1948

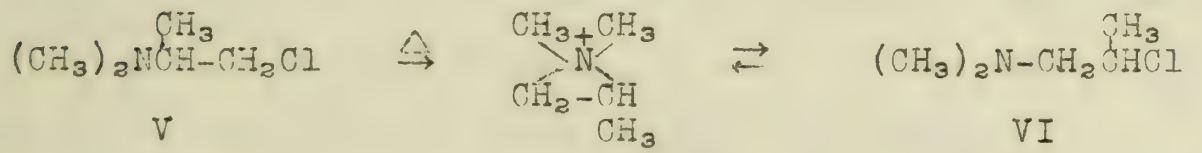
PREPARATION OF AMIDONE

As a synthetic drug to be substituted for morphine, amidone may have widespread use in the near future. Developed by Germany during the war, it was revealed to American scientists in a Department of Commerce report in July 1945 (1). An apparent discrepancy between the expected and reported product has been investigated in several different laboratories.



Two isomeric amino nitriles are formed in the condensation of the amine chloride and diphenylacetonitrile (2). The formation of I is explained by proposing an ethyleneimmonium ion intermediate which would react in a manner similar to that demonstrated for other halogenated alkyl-amines (3,4,5).

More evidence for the intermediate ion has been reported (6,7).



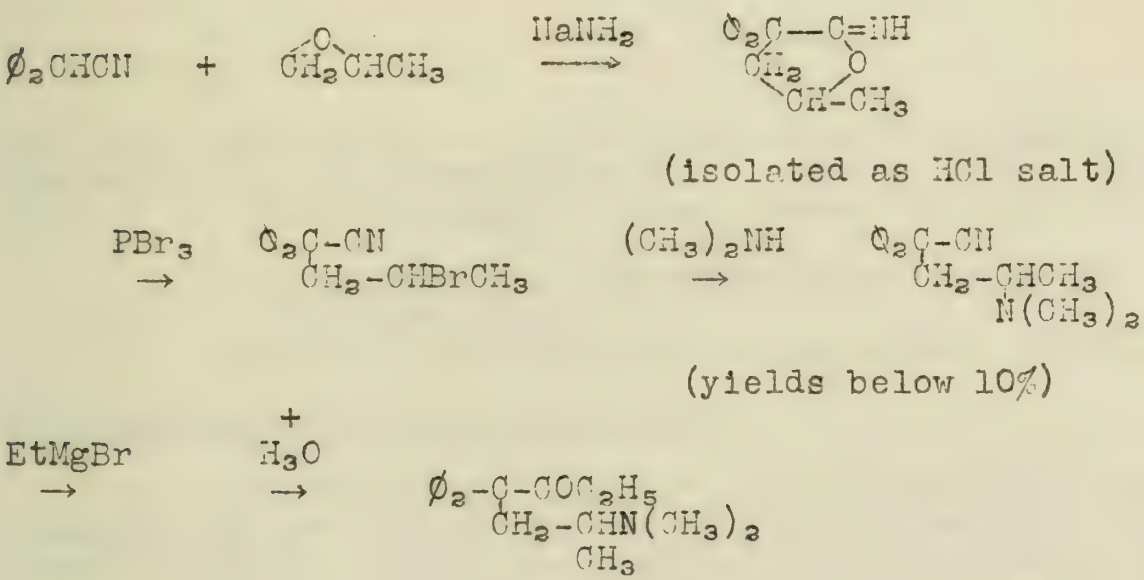
Also the formation of the same mixture of aminonitriles by the action of $\emptyset_2CHCN$, in the presence of $NaNH_2$, on V and/or VI is best explained using the ethyleneimmonium ion intermediate.

Steric and polar factors within the cyclic ion and in the reacting anion govern the course of the reaction. Thus a chloride ion produces predominantly if not completely $(CH_3)_2NCH_2CH(CH_3)Cl$ whereas the relative large anion from $\emptyset_2CHCN$ produces equal amounts of the isomers.

It can readily been seen that the production of two isomers introduces difficulty in the synthesis of amidone.

When Easton and co-workers recently discovered a third isomer (8) after the Grignard reaction this difficulty seemed to increase. The two known structures have been designated amidone and isoamidone. Easton is still investigating the structure of the new isoamidone.

A new synthesis (9) eliminating this difficulty has been carried out by Easton:



(isolated as HCl salt)

(yields below 10%)

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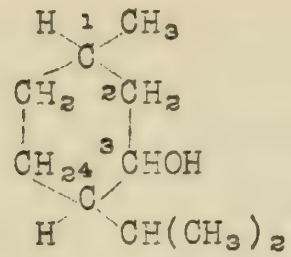
Reported by J. H. Boyer
March 12, 1948

STEREOISOMERISM OF THE MENTHOLS

The menthols are monocyclic secondary alcohols of the structure:



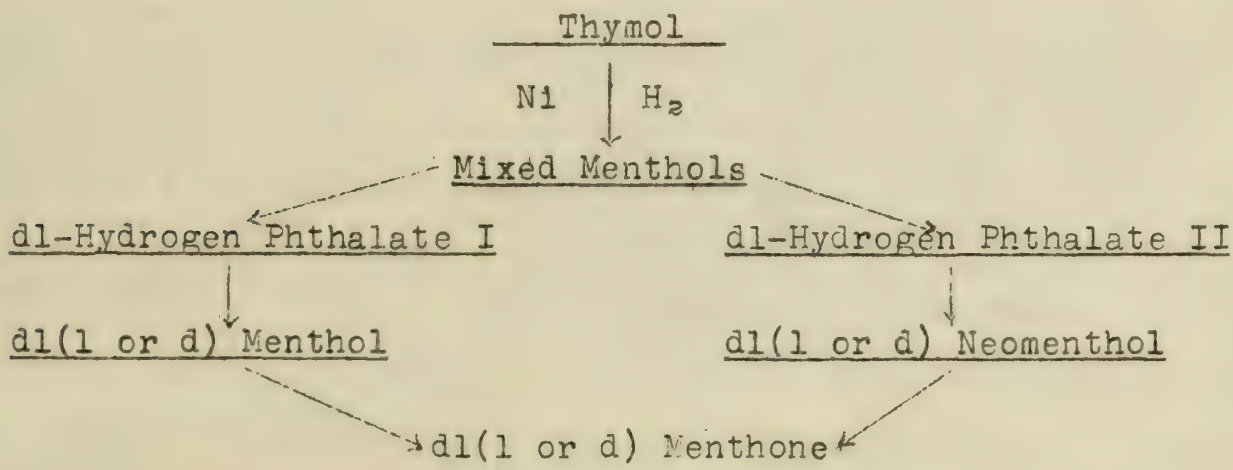
The four inactive forms are designated as dl-menthol, dl-neomenthol, dl-isomenthol and dl-neoisomenthol. Elucidation of the configuration of the various menthols necessitates the following:

1. Assignment of the proper relation of the groups about C(1) and C(4).
2. Relative disposition of the groups about C(3).

<u>Configuration about C(1) and C(4)</u>.

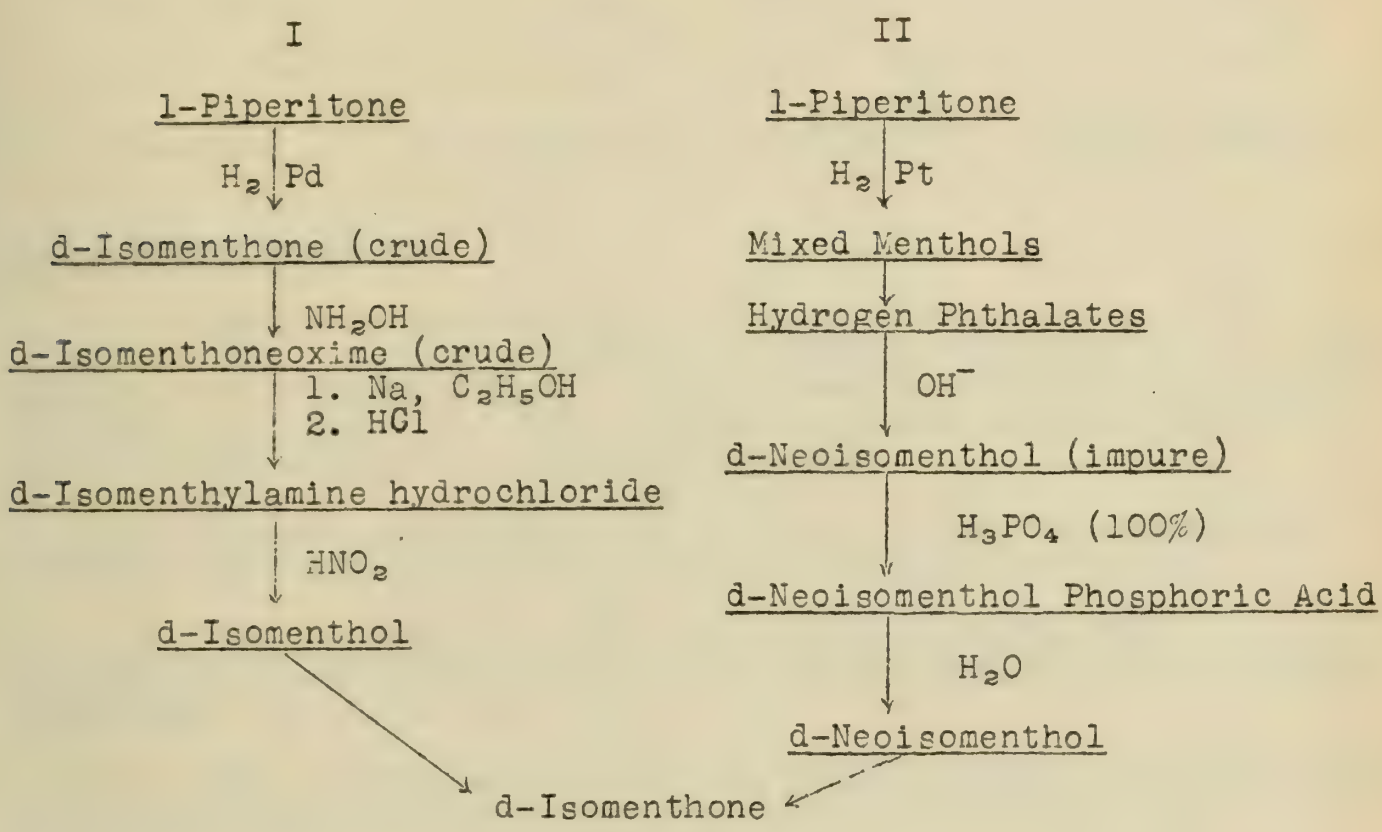
The derived ketones, menthone and isomenthone, are <u>cis</u>-<u>trans</u> isomers, and are fundamental in the stereochemistry of the menthols. They have been assigned the <u>trans</u> and <u>cis</u> structure respectively, since l-menthone possesses a lower density and refractive index (Auwers-Skita Rule) (1). Parachor measurements on the menthones were inconclusive (2, 3), but electrolytic reduction of l-menthone and dl-isomenthone gave the known <u>trans</u> and <u>cis</u> <u>p</u>-menthanes (2, 4).

The spatial structure of these ketones established the <u>trans</u> configuration of the menthol-neomenthol pair of alcohols, since Pickard and Littlebury (5) had effected the following series of transformations:



Optically pure samples of isomenthone, isomenthol and neoisomenthol were not know until Read and his students were able to

effect their preparation. They obtained d-isomenthol and d-neoisomenthol from l-piperitone.

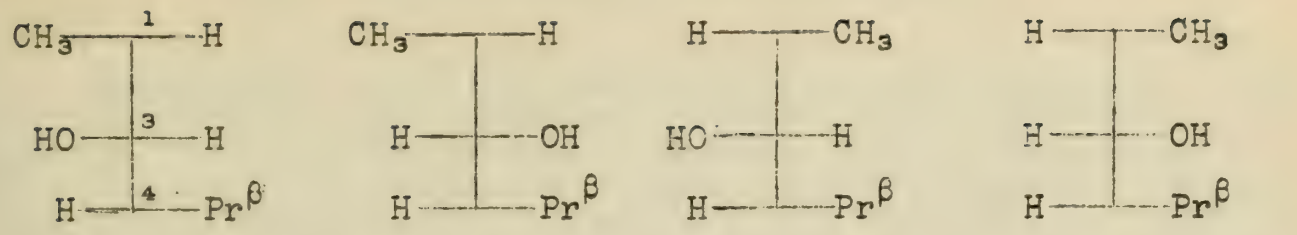


The series of four menthols can thus be separated into two pairs with respect to spatial distribution of groups about C(1) and C(4): trans (menthol and neomenthol) and cis (isomenthol and neoisomenthol).

Configuration about C(3).

The work of Read et al made available pure samples of the d-neo-, d-iso-, and d-neoisomenthols and enabled a systematic study of the asymmetry of C(3). Vavon and Couderc (8) and Zeitschel and Schmidt (9) had shown that in the esterification of l-menthol and d-neomenthol, the rates for the former are greater. Read confirmed this (10) by competitive reactions of pairs of the isomers with various acyl halides in dry pyridine. The p-nitrobenzoyl chloride gave the highest rates: l-menthol (16.5), d-isomenthol (12.3), d-neoisomenthol (3.1), d-neomenthol (1.0). Attributing the difference in reaction velocities to steric influences, Read has assigned to OH(3) and H(4) a trans arrangement in the neomenthols.

The relative configurations of the menthols can be summarized as follows:



l-menthol d-neomenthol d-isomenthol d-neoisomenthol

Independent Evidence.

(1) Catalytic hydrogenation of l-piperitone by specific catalysts (Pd, isopropyl alcohol as solvent, followed by Pt, glacial acetic acid) yielded largely the neoisomers (70% d-neoisomenthol and 25% d-neomenthol). (11). This was predicted from considerations of the mechanism of the reductions.

(2) The esterification rate of trans, l-2 cyclohexanediol monobenzoate is much greater than that of the cis isomer (10).

(3) The neo series of the menthols and menthylamines is easily dehydrated to Δ-3 p-menthene. This can be accounted for by trans elimination of water (10, 12).

(4) The p-toluenesulfonates of the neo-isomers are very easily hydrolyzed, even by minute traces of acid.

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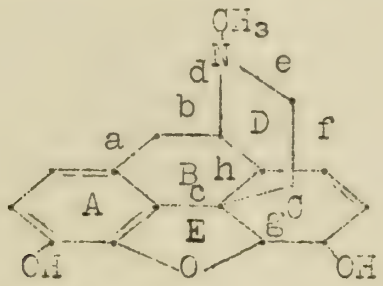
Reported by Frank Verbanac
March 12, 1948

SOME ANALGESICS RELATED TO MORPHINE

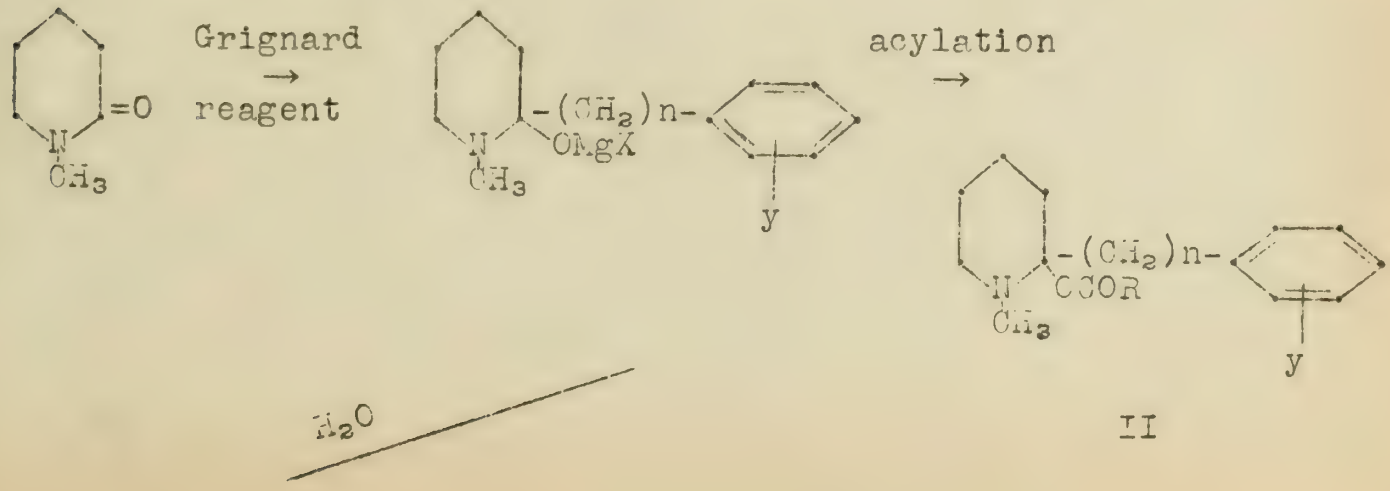
Introduction.--In the search for synthetic compounds to be used in medicine, one method of approach is to simulate or reproduce, to a greater or lesser degree, partial structures of more complex physiologically active compounds found in nature. This method has occasionally met with success; one may cite, for example, the synthetic compounds prostigmin related to physostigmin, syntropan related to atropine, and procaine related to cocaine. This abstract deals with the synthesis by Lee and coworkers (1) of compounds containing partial structures of morphine, to test their analgesic action.



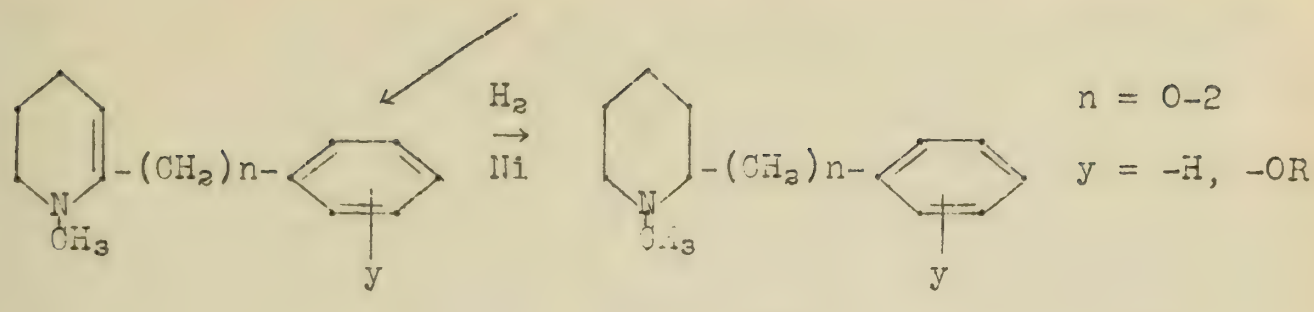
I

Theoretical.--From the skeleton of morphine (I) several partial structures may be extracted, of which the following were considered: Type 1: Rings A and D connected by chain ab give 2-benzyl-N-alkylpiperidines. Type 2: Rings A and D connected by bond c give 4-phenyl-N-alkylpiperidines. Type 3: Rings A and C connected through chain abdefg give (β-phenylethyl)-(β-cyclohexylethyl)-methylamines. Type 4: Rings A and C connected by bond c, and connected to the nitrogen by chain dh give N-substituted 1-aminomethyl-2-phenylcyclohexanes.

Experimental.--The Type 1 compounds studied were of the structures (II) and (III), and were synthesized as follows:



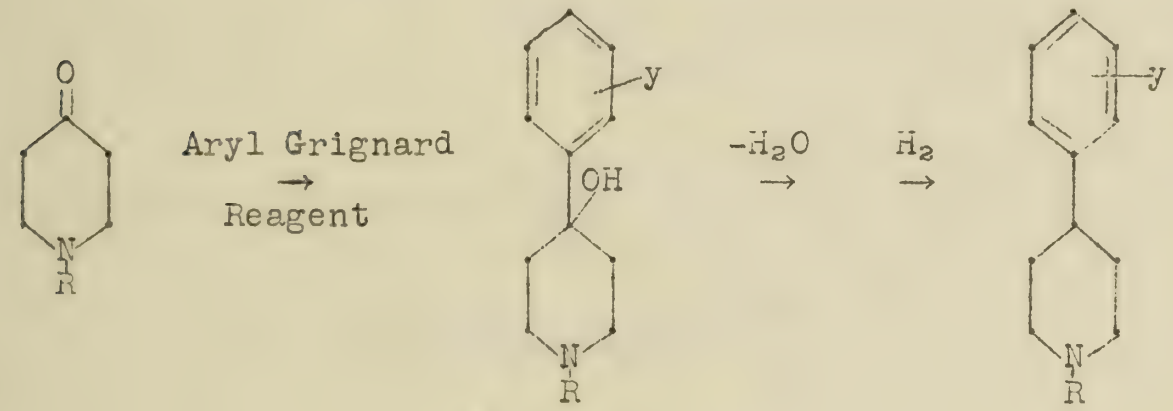
II



III

The 1-methyl-2-substituted piperidinol esters (II, n = 0 or 1) were inactive as analgesics. Compound III (n = 1 or 2) was inactive with hydrogen, hydroxyl, methoxyl, or acyloxyl groups in the para position of the aromatic ring (2). When n = 0, compound III was inactive if unsubstituted or substituted with hydroxyl or acetoxyl groups. With a methoxyl group the compound exhibited low analgesic activity, and with a dimethylcarbamoxyl group somewhat more.

Compounds of Type 2 were synthesized as follows:



IV V

y = -H, -OR, -OH, acyl

VI

The alcohols (IV) had low activity, whereas their unsaturated dehydration products and the hydrogenated compounds (V) had activities about one-fifteenth that of morphine. The esters (VI) had marked analgesic action, the propionyl ester having the optimal activity (3). When R is methyl, pronounced catelepsy results from the analgesic dose, but when the N-alkyl chain is lengthened, the cateleptic effect at analgesic doses is lowered. These compounds have activity comparable to that of morphine, but unfortunately are unstable in aqueous solution. Substitution of the phenyl ring in IV, V, or VI reduced the effectiveness of these compounds.

The Type 3 compounds studied were synthesized as follows:

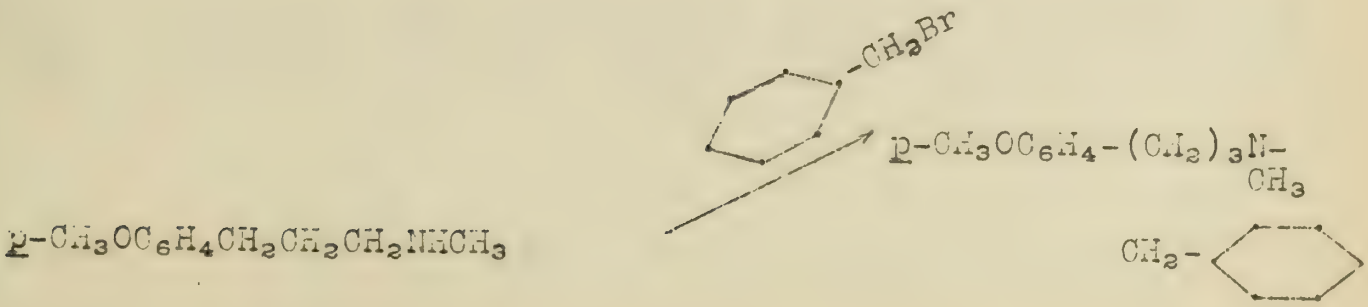
A. $\underline{p}\text{-}CH_3O\text{-}C_6H_4\text{-}CH_2CN \xrightarrow[NH_3]{H_2,Ni(R)} \underline{p}\text{-}CH_3O\text{-}C_6H_4\text{-}CH_2\text{-}CH_2\text{-}NH_2$

$\xrightarrow{C_6H_5CHO} \xrightarrow{(CH_3)_2SO_4} \xrightarrow{H_2O} \underline{p}\text{-}CH_3O\text{-}C_6H_4\text{-}CH_2\text{-}CH_2\text{-}NHCH_3$

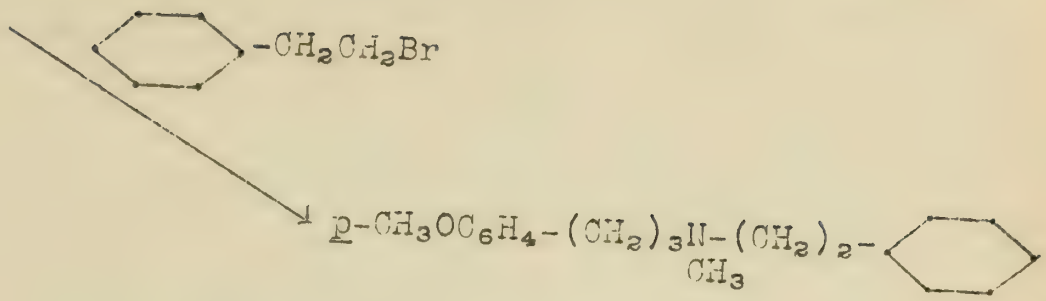
VII

B. $\underline{p}\text{-}CH_3OC_6H_4CH{=}CHCO_2H \xrightarrow[H_2]{Ni(R)} \underline{p}\text{-}CH_3OC_6H_4CH_2CH_2CO_2H \xrightarrow{SOCl_2}$

$\xrightarrow{NH_3} \xrightarrow{P_2O_5} \underline{p}\text{-}CH_3OC_6H_4CH_2CH_2CN \xrightarrow[\text{above}]{\text{same as}}$



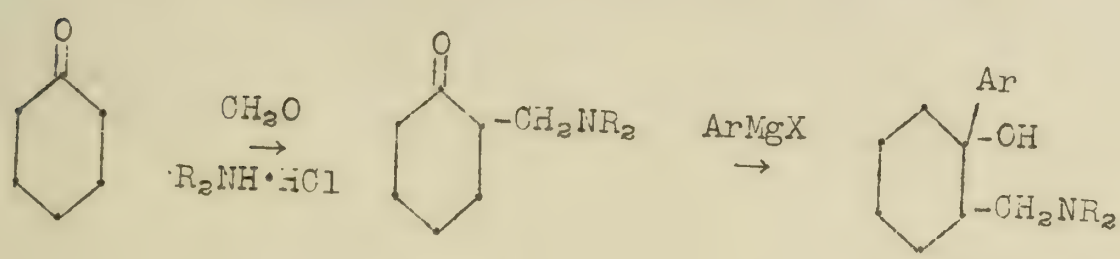
VIII



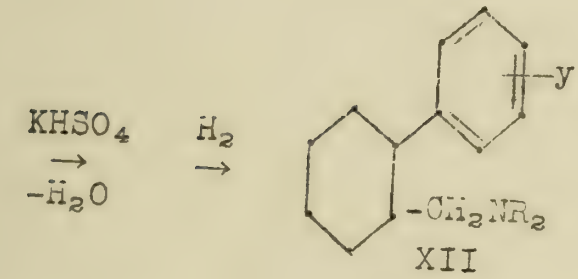
IX

The para-methoxyl group of VII, VIII, and IX was then hydrolyzed and the effects of acetylation and etherification studied. The compound with the greatest activity (about one-seventh that of morphine) was the one resembling most closely the type formula, namely, (β-p-hydroxyphenylethyl)-(β-cyclohexylethyl)-methylamine. Blocking of the hydroxyl group or variation of the alkylene chain lengths decreased the activity.

Type 4 compounds were prepared as follows:



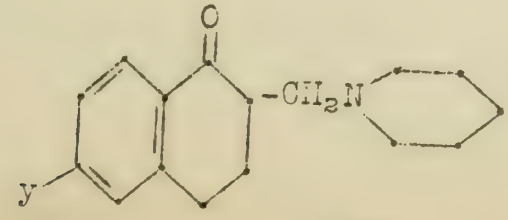
X XI



XII

y = -H, -OH, -OR, -OCOR, -R

The end products (XII) demonstrated little or no activity, but some of the intermediates showed activity of about one-seventh that of morphine. The most active were of the type



XIII

y = -H, -OCH3

Reduction to the alcohol had little effect on XIII; acetylation decreased the activity.

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2. Lee and Freudenberg, J. Org. Chem., 9, 537 (1944).
3. Jensen, Lindquist, Rekling, and Wolffbrandt, Dansk. Tids. Farm., 17, 173 (1943); (cf., C.A., 39, 2506 (1945).

For previous work:

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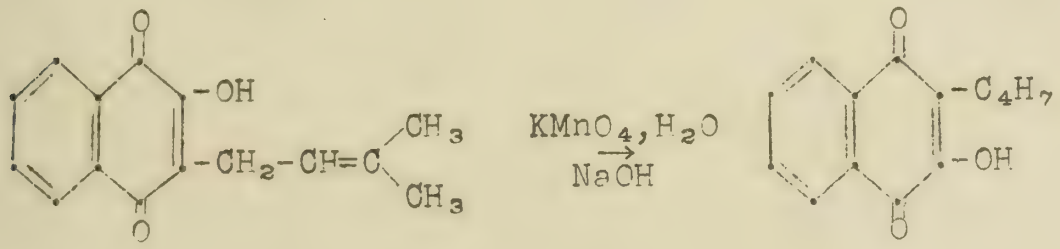
Reported by Harold J. Watson
March 12, 1948

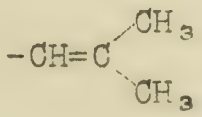
THE HOOKER OXIDATION AND RECENT APPLICATIONS

In 1936 there appeared in the Journal of the American Chemical Society a series of eleven papers (1) by S. C. Hooker, published posthumously, describing the results of seventeen years of research in his own private laboratory. In attempts to degrade lapachol (I) and related naturally occurring derivatives of 2-hydroxy-1,4-naphthoquinone by oxidation he encountered the following unexpected reaction:



I II

Comparison of (II) and its hydrogenation-product with their known isomers containing other mono-unsaturated and saturated four-carbon side chains proved the butenyl group to be constituted as follows:

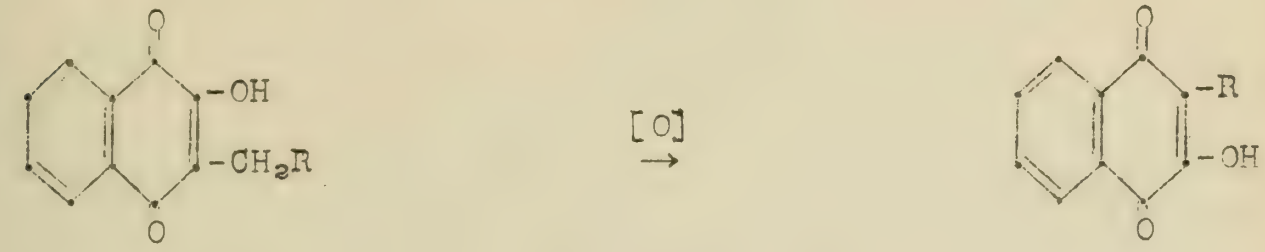


Thus (I) had lost the methylene-group adjacent to the quinone-ring, while the olefinic bond remained unaffected. The hydration-product of lapachol, similarly, could be degraded to its lower homologue without any other apparent change in the molecule.

In a more thorough study of the reaction Hooker prepared both the 3-n-heptyl and the 3-hydrocinnamyl derivatives of 2-hydroxy-1,4-naphthoquinone, and by a series of permanganate oxidations corresponding to the number of $-CH_2-$groups in the side-chain, degraded them to the parent-compound and to 3-phenyl-2-hydroxy-1,4-naphthoquinone, respectively. He synthesized all expected intermediates of both degradations directly by unequivocal methods, and demonstrated identity of the degradation-products with the authentic samples.

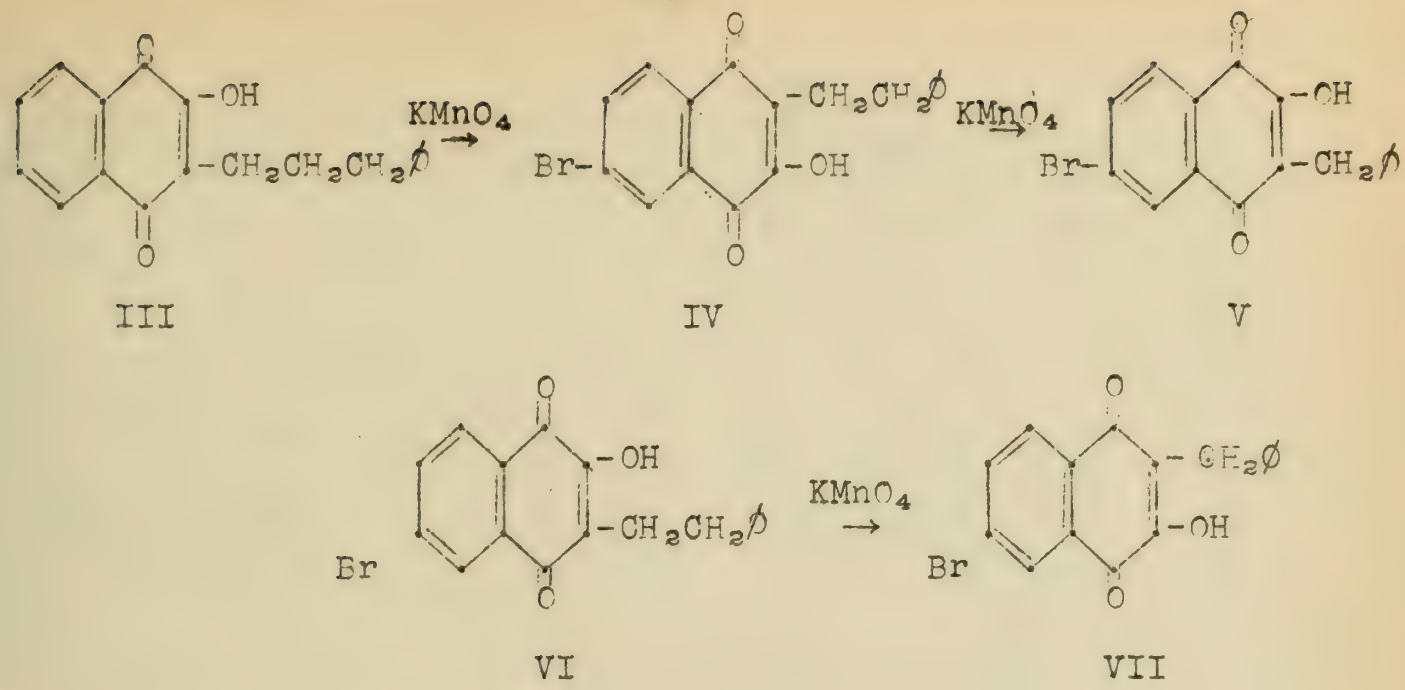
Yields obtained in all reactions of compounds with saturated side-chains varied from 70 to 80%. Oxidations were run in strongly alkaline solutions. Olefinic derivatives, however, could be degraded to their lower homologues in only 35 to 40% yields in slightly basic medium. Fieser (3) has recently employed the reaction to synthesize alkyl derivatives of 2-hydroxy-1,4-naphthoquinone which were otherwise inaccessible. He improved the method by running each oxidation in two steps, employing alkaline hydrogen peroxide in the first and alkaline copper sulfate in the second.

The reaction appears to be applicable only to alkyl derivatives of 2-hydroxy-1,4-naphthoquinone. The following table summarizes results obtained by Hooker (H) and Fieser (F).



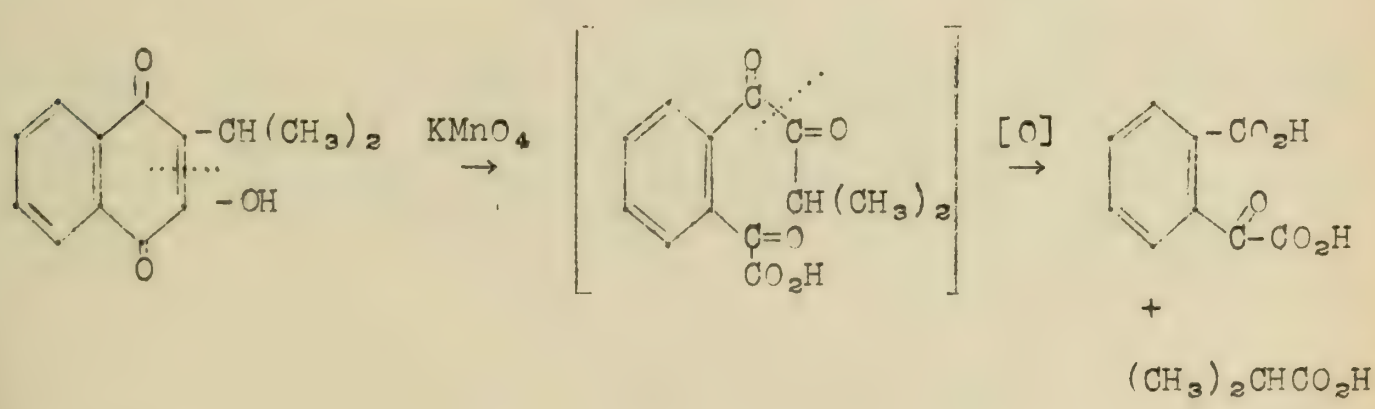
R	Yield (%)	Method
$-CH=CH_2$	(low)	H
$-CH=CHCH_3$	(low)	H
$-CH=CH\ \emptyset$	(low)	H
$-CH=C(CH_2OH)(CH_3)$	(low)	H
$-CH_2CH=CHCH_3$	76 (pure)	F
$-(CH_2)_3$-cyclohexyl	82 (pure)	F
$-(CH_2)_3-C_6H_4OC_6H_5$-p	86 (pure)	F
$-CH_2-C_6H_{10}C_6H_{11}$-trans	70 (pure)	F
$-(CH_2)_{14}CH_3$	78 (pure)	F
$-(CH_2)_9\ \emptyset$	72 (pure)	F
$-(CH_2)_8CO_2H$	78 (crude)	F

<u>Mechanism</u>. Without experimental evidence, Hooker proposed that the reaction took place in two distinct steps: a) cleavage of the quinone-ring, and b) subsequent ring-closure with elimination of carbon-dioxide, the hydroxyl and alkyl groups reversing their positions. In an early study Fieser (2) fully confirmed Hooker's view:



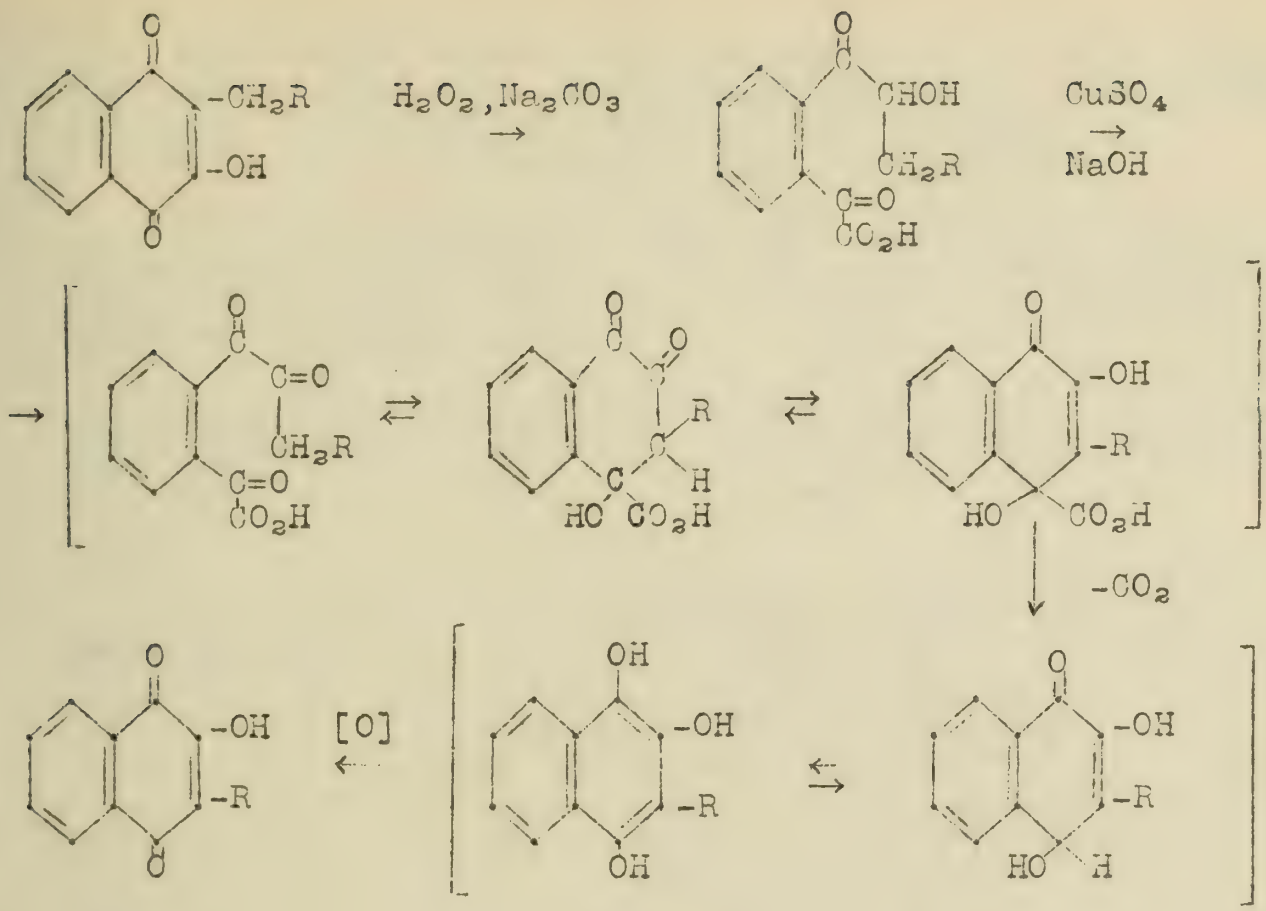
The position of the alkyl groups in III, V, and VI was known by unequivocal synthesis; IV and VI, and V and VII were shown to be non-identical pairs. As additional proof 2,6-dimethyl-3-hydroxy-1,4-naphthoquinone was degraded to 6-methyl-2-hydroxy-1,4-naphthoquinone, which was also prepared by a direct route from β-methylnaphthalene.

The mechanism of ring-cleavage was demonstrated on an alkyl derivative branched in the position adjacent to the ring, whose cleavage-product would be incapable of subsequent ring-closure in the normal way:



The intermediate 1,2-diketo-compound (IX) was further cleaved by oxidation, and phthalonic and isobutyric acids were isolated.

The complete mechanism of cleavage as well as ring-closure was finally elucidated by Fieser (3) in the course of work on a war-time project directed toward the synthesis of 2-hydroxy-1,4-naphthoquinone derivatives as potential antimalarials. He proved that each degradation included two oxidative steps, which Hooker had also suspected but could not demonstrate:



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3. Fieser, Abstracts, 10th Organic Symposium, June 1947, p. 12ff.; Record Chem. Progress (Kresge Hooker Sci. Lib.), 7, (3+4), 26 (1946).

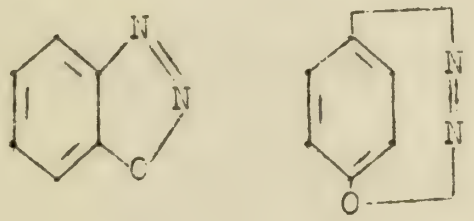
Reported by Frank X. Werber
March 12, 1948

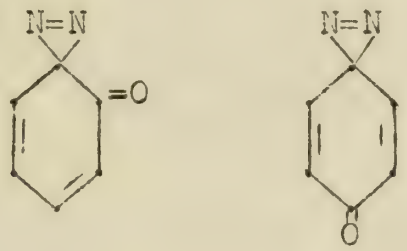
DIAZO-OXIDES

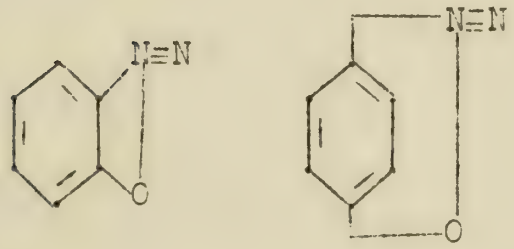
Diazo-oxide is the name most commonly given to certain diazotized aminophenols and aminonaphthols. For this reason, they sometimes are called diazophenols and diazonaphthols or, less frequently, quinonediazides and diazo-anhydrides.

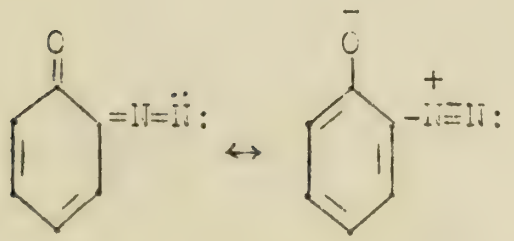
The first diazo-oxide was made by Griess (1) in 1858 by diazotizing picramic acid. The compound was reasonably stable and differed in its chemical and physical properties from the expected diazonium salt.

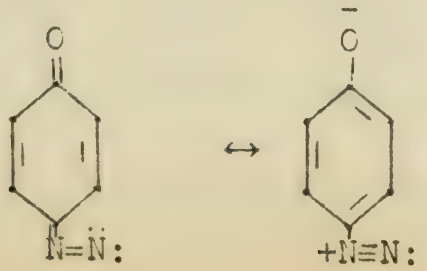
Concepts of Structure.--The following structures have been postulated, each in agreement with the structural theories of that time.

Bamberger (2)  (1895)

Wolff (3)  (1900)

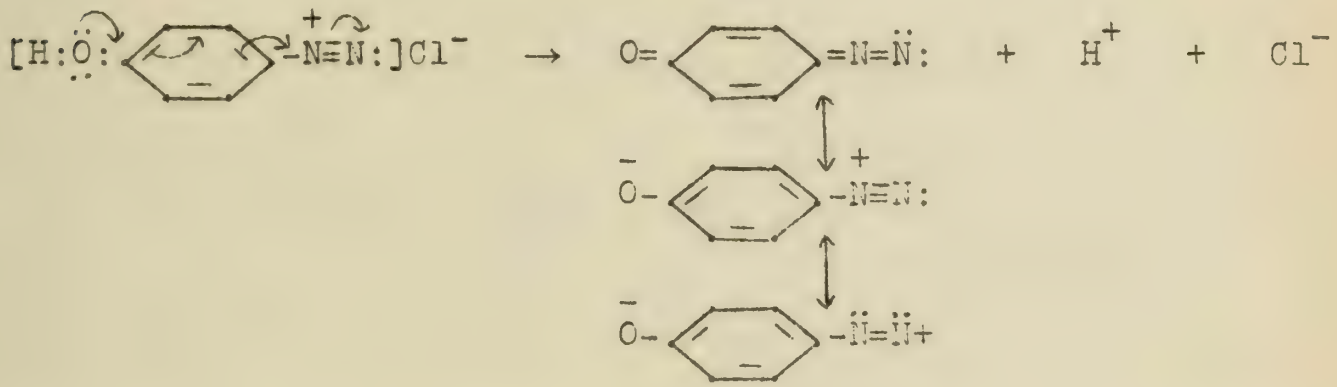
Klemenc (4)  (1914)

Hodgson and Marsden (5)  (1943)



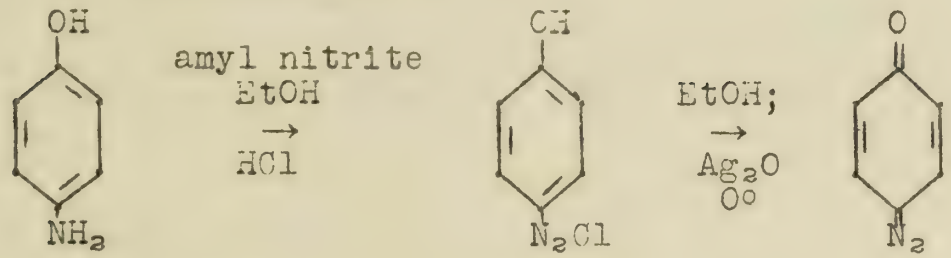
The formulae proposed by Hodgson and Marsden have been substantiated by convincing ultraviolet absorption spectra studies that give proof of the presence of the ketonic and quinonoid structure and the absence of a -O-N=N- linkage (6,7).

Synthesis.--Usually, diazo-oxides result from the diazotization of ortho- or para-aminophenols and naphthols, sometimes directly and sometimes by the addition of water, alkali, sodium acetate, or silver oxide to the diazonium compound. The diazo-oxides can be formulated as coming from ionization of the phenolic group, which is intensified by the electron-attracing diazonium group, followed by resonance of the ion thus formed. Quinonoid structure is not possible for the meta form; hence normal diazonium compounds rather than diazo-oxides are obtained.

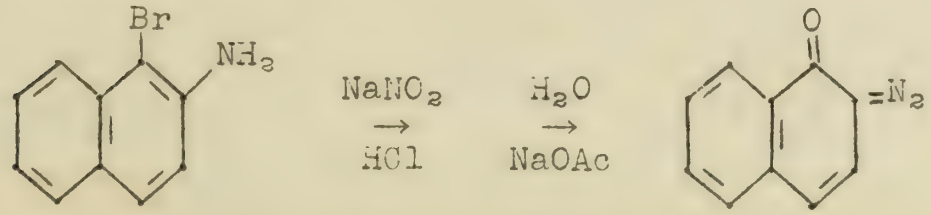


Thus, the removal of either the proton or anion facilitates the formation of the diazo-oxide.

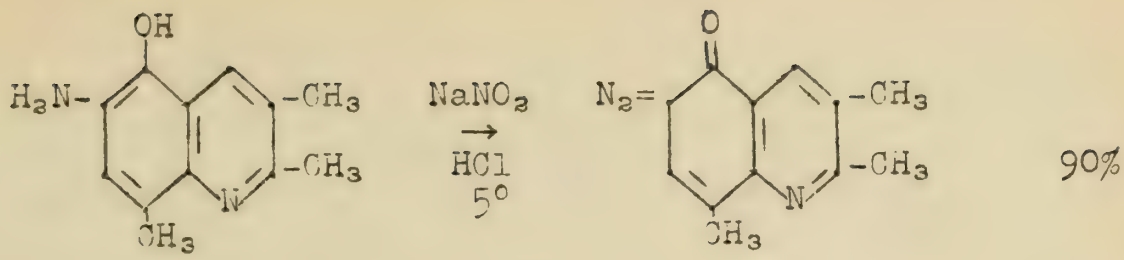
1. p-benzoquinonediazide (7).



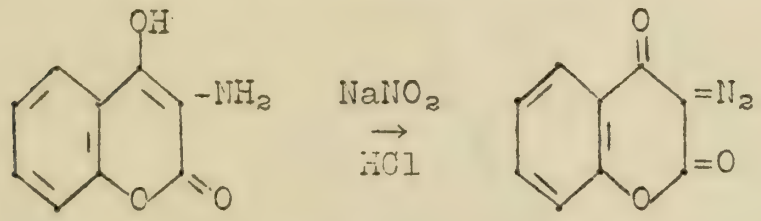
2. 1,2-naphthoquinonediazide-2 (7).



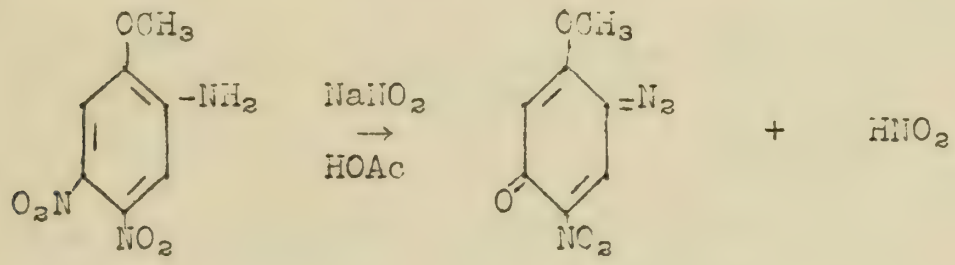
3. 2,3,8-trimethylquinoline-6-diazo-5-oxide (8).



4. 3,4-diazocoumarinoxide (9).



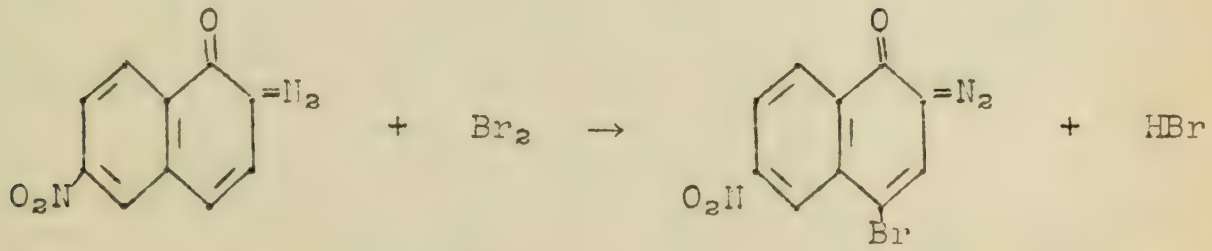
5. 2-methoxy-5-nitro-p-benzoquinonediazide-1 (10).

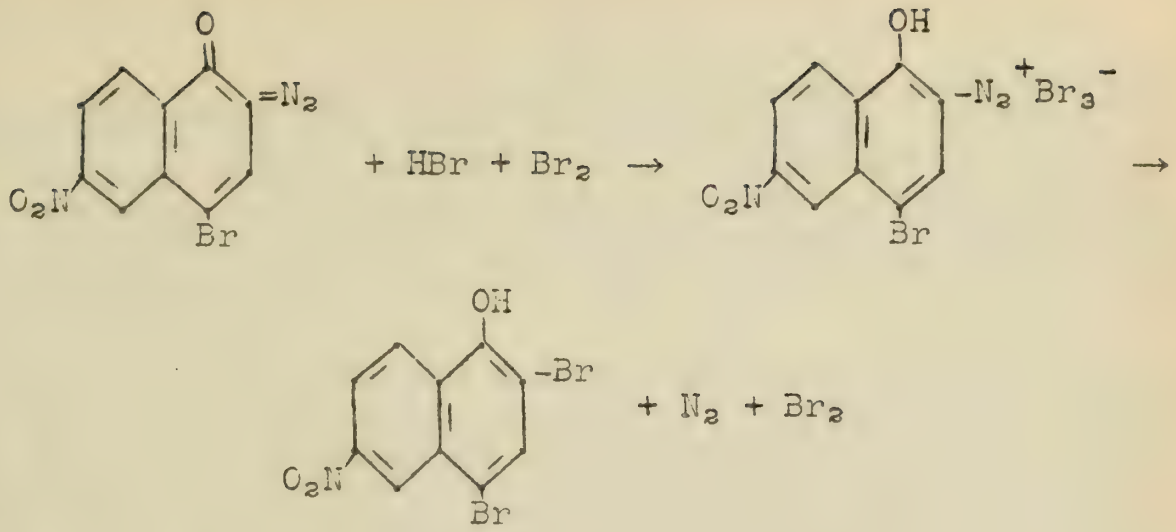


Reactions.--Diazo-oxides are sparingly soluble in water, non-ionized, colored, and couple very slowly. They can be isolated as solids and are distinctly more stable than most aromatic diazo derivatives. However, they often decompose on standing or heating and detonate when struck a sharp blow.

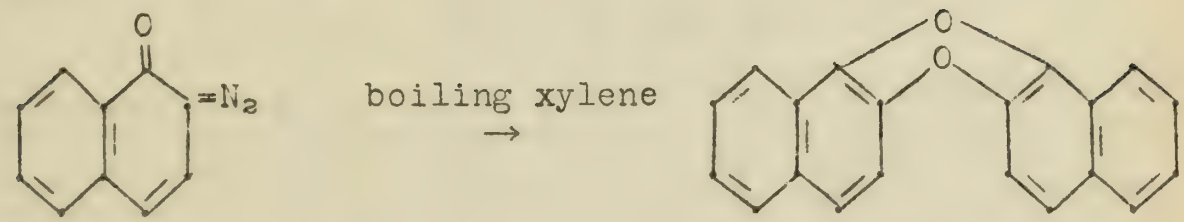
The Sandmeyer and Gattermann reactions proceed smoothly to yield the corresponding halophenol or halonaphthol (11). The diazonium group can be replaced by hydrogen with copper and ethyl lacohol (12). Some interesting reactions of diazo-oxides are given below.

1. Bromination (13).

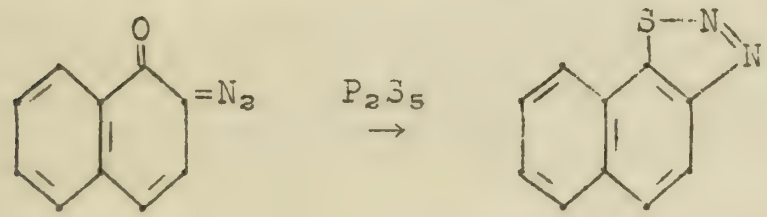




2. Bis-naphthalene oxide (14).



3. 5,4-(1',2'-naphtho)-1,2,3-thiadiazole (14).



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Reported by William C. Wildman
March 19, 1948

THE USE OF NINETY PERCENT HYDROGEN PEROXIDE

The Stability of 90% Hydrogen Peroxide.--Pure concentrated hydrogen peroxide has been shown to be very stable. In fact, efforts to detonate this material by various devices have failed. By using suitable precautions to maintain purity ninety percent hydrogen peroxide is considered to be safe enough to handle so that it is now shipped in tank cars and stored in tank farms much as other liquids are.

In spite of the fact that the decomposition of hydrogen peroxide is a strongly exothermic reaction, there is very little tendency for it to decompose at room temperature in the absence of catalysts. Chromium, copper, lead, mercury, and iron salts have been shown to be potent catalysts for this decomposition. These catalysts are especially potent in alkaline hydrogen peroxide. Thus, for commercial purposes 99.6% pure aluminum is recommended for storage and handling of concentrated hydrogen peroxide. Pyrex glass is suitable in the laboratory.

Two types of materials have been shown to be effective as stabilizers of concentrated hydrogen peroxide. One type forms complexes with the metals which catalyze the decomposition of hydrogen peroxide. The second type seems to adsorb these metals strongly. Examples of these two types are pyrophosphates and hydrous stannic oxide, respectively.

Solubility.--Besides being completely miscible in liquids which are completely miscible in water, ninety percent hydrogen peroxide shows remarkable solubility in certain other organic materials. This property is one which makes concentrated hydrogen peroxide useful in organic reactions.

Toxicity.--Vapors of hydrogen peroxide are not poisonous, but are irritating to the eyes and nose. Concentrated liquid hydrogen peroxide will cause the skin to blister if not washed off immediately.

Fire Hazard.--In the absence of decomposition catalysts even ninety percent hydrogen peroxide will not start a fire with common combustible materials in the laboratory such as cotton and wood. However, since there are usually traces of metallic contaminants, spilled concentrated hydrogen peroxide is a definite fire hazard and should be washed away with plenty of water. When the concentration of hydrogen peroxide is less than 60%, there is no fire hazard.

Explosion Hazard.--Pure concentrated hydrogen peroxide is stable twoard detonation. Substances easily oxidized or alkaline in nature may react spontaneously and violently. Many organic materials show no particular reactivity. This is particularly true of materials which have low mutual solubility with hydrogen peroxide. No solutions have been found which will detonate if the 90% hydrogen peroxide is less than 30% by volume.

Recommended Laboratory Equipment.--Pyrex glassware which has been thoroughly cleaned of oxidizable and metallic contaminants may be used safely. Silicone lubricants and Koroseal or Polythene gaskets are safe to use. Mercury thermometers should be avoided.

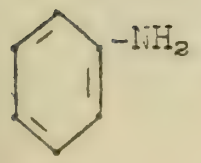
Applications to Organic Chemistry.--As indicated in the organic seminar last semester, 90% hydrogen peroxide converts organic acids rapidly to the corresponding peracids which may be used as hydroxylating agents for olefins. Hydrogen peroxide alone gives no reaction with olefins.

$$RCH{=}CHR + RCOO_2H \rightarrow \underset{\substack{OH \\ OCOR}}{RCHCHR} \xrightarrow{H_2O} \underset{\substack{OH \\ OH}}{RCHCHR}$$

Ninety percent hydrogen peroxide may be used as an oxidizing agent. The advantages of using concentrated hydrogen peroxide in oxidation reactions are the speed of reaction as compared to dilute hydrogen peroxide and the freedom from inorganic by-products other than water.

The oxidation of aliphatic primary amines with concentrated hydrogen peroxide is a vigorous but undefined reaction. However, diethylamine and triethylamine give diethylhydroxylamine and triethylamine oxide, respectively. These reactions may be carried out with either dilute or concentrated hydrogen peroxide. In the case of the oxidation of diethylamine the product is more easily isolated when concentrated hydrogen peroxide is used. This advantage is in addition to the usual advantage of speed.

Azoxybenzene may be conveniently prepared from aniline in an 85% yield with peracetic acid made with 90% hydrogen peroxide. If dilute hydrogen peroxide is used, the yield is considerably poorer



$$\xrightarrow[CH_3COOH]{90\%\ H_2O_2} C_6H_5{-}\underset{O}{N}{=}N{-}C_6H_5 \quad (85\%) \quad + \quad C_6H_5NO_2 \quad (15\%)$$

$$\xrightarrow[CH_3COOH]{\text{dilute } H_2O_2} C_6H_5{-}\underset{O}{N}{=}N{-}C_6H_5 \quad (43\%) \quad + \quad C_6H_5NO \quad (57\%)$$

No other oxidizing agent has been reported to give this reaction in significant yields. Without acetic acid 90% hydrogen peroxide gives aniline black products.

Hydrazobenzene may be oxidized stepwise to azoxybenzene in a

few hours with 90% hydrogen peroxide. As much as a week may be required with 30% hydrogen peroxide.

$$C_6H_5NHNHC_6H_5 \xrightarrow[23^\circ C]{90\%\ H_2O_2} C_6H_5N{=}NC_6H_5 \quad 100\%$$

$$C_6H_5N{=}NC_6H_5 \xrightarrow[CH_3COOH,\ 70^\circ C]{90\%\ H_2O_2} C_6H_5\underset{O}{N}{=}NC_6H_5 \quad 100\%$$

β-Naphthol is converted to o-carboxycinnamic acid in good yields with hydrogen peroxide. Ninety percent hydrogen peroxide requires five hours and 30% hydrogen peroxide requires a week.

Ninety percent hydrogen peroxide gives certain other reactions which may be of interest only because they might lead to side reactions when it is used in other reactions. These are summarized below.

Ethyl alcohol is oxidized only in the presence of catalytic amounts of ferric salts.

Aldehydes are oxidized to acids.

Certain aromatic hydrocarbons may be converted to the corresponding quinones. Thus, durene is oxidized to duroquinone and anthracene to anthroquinone. However, both of these oxidations are made in better yields by other methods.

Paraffins, the methyl side chain in toluene, and alicyclics are not attacked.

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Reported by P. H. Aldrich
March 19, 1948

ETHYLENIMINES

Introduction.--Not much work has been reported on ethylenimines, the nitrogen analogs of ethylene oxide, primarily because of the lack of a good general method of preparing them. The preparation and reactions of some simple imines, and some substituted ethylenimine ketones are reported here.

Preparation.--The synthesis of cyclic polymethylenimines was first attempted by Ladenburg (1) by heating diamine dihydrochlorides. Although pyrrolidine and piperidine were obtained easily from the 1,4- or 1,5-diamines, trimethylenediamine gave a low yield of trimethylenimine and ethylenediamine yielded only piperazine. The treatment of certain olefins with phenylazide gives imines, particularly if the double bond is in a bicyclic system (2). Simple aliphatic olefins give mostly anils, while styrene gives a mixture of the anil and imine.

The most general method of preparation of imines is the treatment of β-haloamines with alkali or silver oxide (3,4,5,6). The yield is improved by the use of the hydrochloride salt.

$$\emptyset CHClCH(\emptyset)NH_2 \cdot HCl \xrightarrow[EtOH]{KOH} \emptyset CH\text{-}CH\emptyset \quad (NH) \qquad 96\%$$

The monophenyl derivative was prepared in 70% yield. Often the haloamine is prepared from the alcohol by refluxing it with hydrochloric acid or thionyl chloride. This procedure is particularly useful when the imine cannot be made directly from the alcohol. Aliphatic imines are often best prepared by treating a β-aminoalcohol with sulfuric acid and distilling the ester over caustic (7,8,9). Ethylenimine itself is made industrially in this manner, and imines containing up to twelve carbons have been reported. The yields range from 30 to 65%.

Imines may be isolated from the reaction of phenylmagnesium bromide on oximes, and the course of the reaction has been postulated according to the following series of reactions (10).

$$\emptyset C(NOH)C_2H_5 \xrightarrow[\emptyset CH_3]{\emptyset MgBr} \emptyset\text{-}C(NOMgBr)\text{-}C_2H_5 \xrightarrow{\emptyset MgBr} \emptyset_2C(NOMgBr)(MgBr)C_2H_5 \rightarrow$$

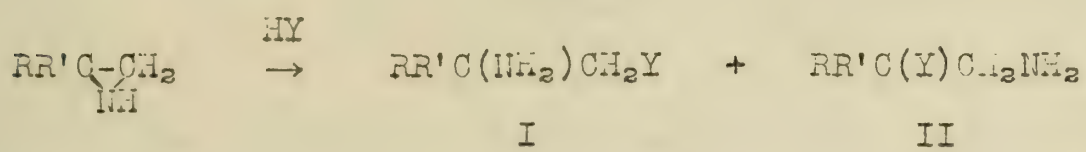
$$\emptyset_2C(NMgBr)\text{-}CHCH_3 \rightarrow \emptyset_2C(NH)\text{-}CHCH_3$$

The yield is about 30%. The best results were obtained by running the reaction in toluene and hydrolyzing the complex with aqueous ammonium chloride. The use of ether as the solvent and acidic hydrolysis gave mainly the aminoalcohol.

The action of diphenylketene on N-phenylbenzaldoxime has been reported to yield 1,2,2,3-tetraphenylethylenimine (11).

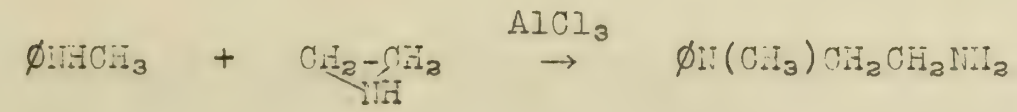
Ethylenimines are generally colorless compounds which are unaffected by potassium permanganate and bromine, and which form alkali-insoluble benzenesulfonamides. These facts form a basis for the cyclic, secondary amine structure. Further evidence for this is the preparation of optically active d- and l-2,3-diphenylethylenimine from d- and l-chloroaminodibenzyl (4). Only geometric isomers would be possible from the vinylamine structure. Ethylenimine itself is a very toxic compound, and should be handled with great care (12). No reports are available on the toxicity of the higher homologs.

Reactions.--The reactions of imines closely resemble those of epoxy compounds, and the ring can be opened in two ways (13).



In general, the compounds of type I predominate, although occasionally both types are obtained. If HY is the imine, polymerization may occur, but this reaction may be reduced by the use of high temperature and pressure. Hydroxy- and haloamines can be readily made by treating the imine with water or HX, but this is seldom of value as a preparative method since it would probably be a reversal of the imine synthesis. Both high and low pressure procedures have been reported for hydrogenating 2,2-dimethylethylenimine to t-butylamine, which cannot be made readily by other methods (14,15). In this case none of the product of type II, isobutylamine, was found.

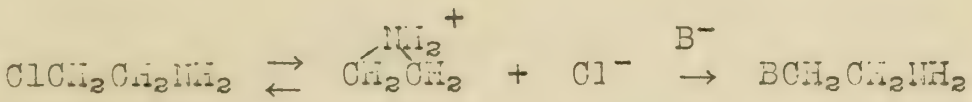
Many diamines which are otherwise difficult to prepare can be made by reacting the appropriate amine and imine (16).



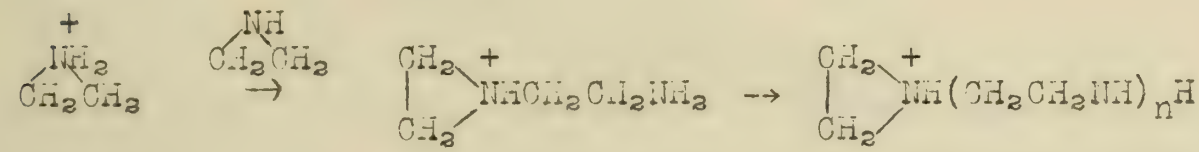
The reaction with secondary amines is run in benzene at about 90°C., while with primary amines a temperature of 180°C. is required, with tetralin or biphenyl as the solvent. The yields are 77 to 89%. Primary amines with ammonium chloride as catalyst (temp. 25-100°C., pressure 10-60 atm.) give analogous compounds (13). The yields are 40-85%, but there is no reaction without the ammonium chloride.

The polymerization of ethylenimine takes place readily in the presence of an acid catalyst, often producing explosions when

run at room temperature (9,17). The products are linear poly secondary amines containing from 25 to 100 monomer units, and are thought to be formed by the bimolecular reaction of ethylenimine and ethylenimonium ions.

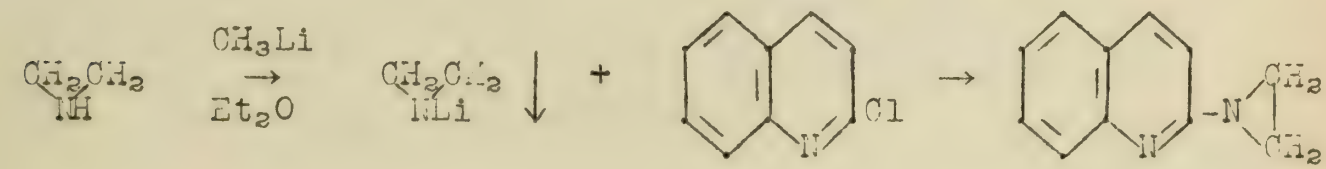


If ethylenimine is the base the reaction can continue, giving a polymer. An alternative mechanism, corresponding to the polymerization of ethylene oxide, has been suggested for the reaction of

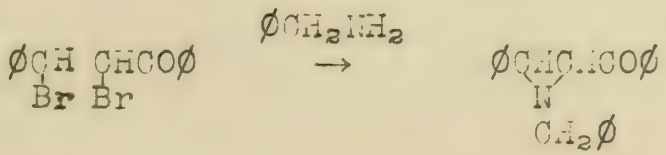


ethylenimine and ammonia under pressure (18). Ethylenimine homologs polymerize slowly and incompletely if no $-CH_2$ is present. Cleavage occurs between the nitrogen and $-CH_2$.

Miscellaneous Reactions.--Many condensation products of ethylenimine and carbon disulfide (19), phthalimide (20), isocyanates (21,22), etc. have been reported in the patent literature, but the products have generally not been characterized. Reaction with ketene (23) and 1,6-hexanedithiol (24) gives the expected ethylenamides and β-aminosulfides, and 2-ethylenimino-quinoline has been prepared from the lithium imide (25).



Ethylenimine Ketones.--Many highly substituted ethylenimine ketones have been prepared by the reaction of amines and β-bromobenzalacetophenone or α,β-dibromobenzylacetophenone (26,27,28).



The reaction appears to be fairly general, although the yields vary considerably (20-95%). These ketones give the normal reactions for both the carbonyl and the imine groups, although treat-

ment with aqueous HBr gives the α-bromo-β-aminoketone, while with HBr in dry benzene the β-bromo-α-aminoketone is produced.

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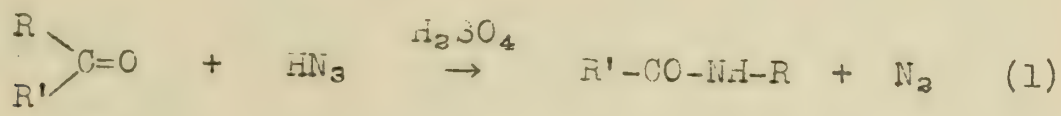
Reported by C. H. Young
March 19, 1948

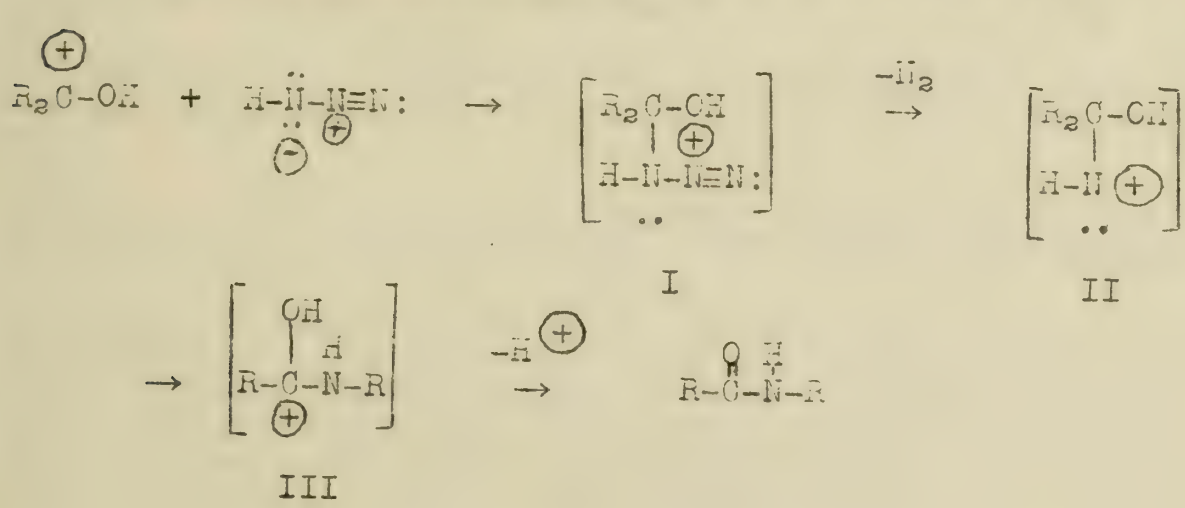
THE MECHANISM OF THE SCHMIDT REACTION

The Schmidt Reaction includes the reactions of carbonyl compounds with hydrazoic acid in the presence of strong acids. The overall reaction is:

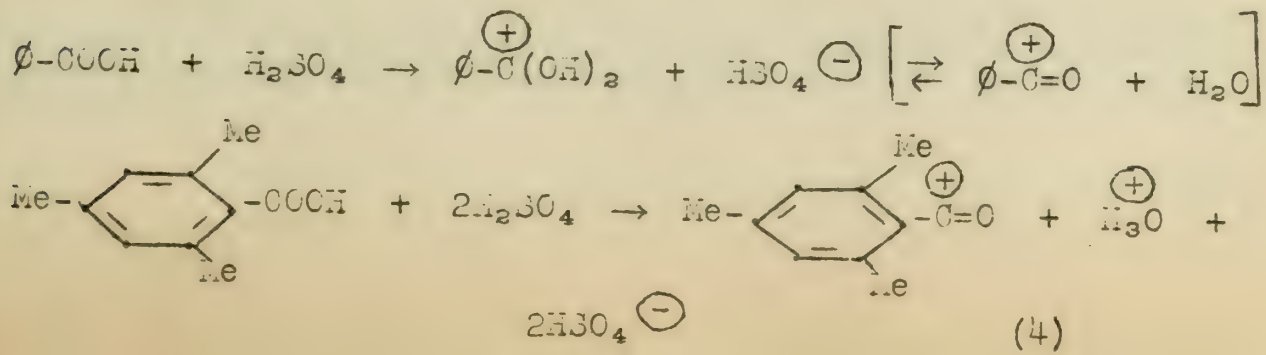


If R' is OH carbon dioxide is evolved and the product is RNH_2. Aromatic amination by the same reagents is not included since it has been shown to take place by a different mechanism involving the NH or $NH_2^{\oplus}$ radical (1).

Schmidt himself believed that amination of carbonyl compounds was effected by the NH radical, perhaps involving the formation and rearrangement of the oxime (2), but this view has been discredited since hydrazoic acid does not decompose to NH and N_2 and oximes do not rearrange under the conditions used (3,4). A carbonium ion mechanism has now been postulated (5,6):



Excess hydrazoic acid produces tetrazoles, presumably by the addition of HN_3 to II with subsequent rearrangement and cyclization. In support of a carbonium ion mechanism Newman and Gildenhorn (5) have found that in 100% sulphuric acid trimethyl benzoic acid reacts at 0°C whereas benzoic acid itself requires a higher temperature. It is known that the acids ionize as follows (7):



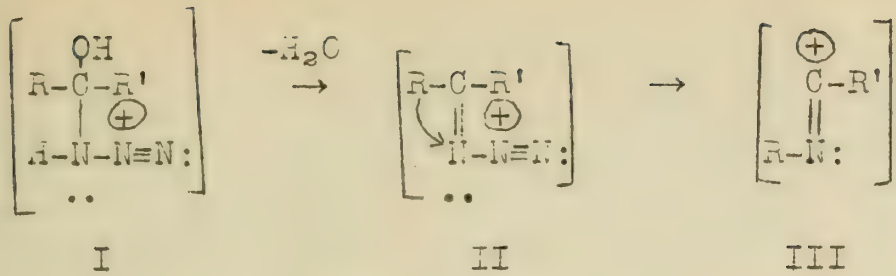
The authors postulate that at least the oxocarbonium ion of equation (4) reacts more readily with HN_3, a higher temperature being necessary for benzoic acid either to make the less reactive dihydroxycarbonium ion react or to shift the equilibrium in equation (3). Briggs and Lyttleton (8) have shown that the rate of evolution of nitrogen is inversely proportional to the dissocation constant of the acid in the case of substituted benzoic acids. This can also be exaplined by the proposed mechanism. When trialkyl acetic acids, [R_3C-COOH], are aminated by the Schmidt method, products are formed which lead to the assumption of an intermediate trialkylcarbonium ion [$R_3C^{\oplus}$] (6). This is shown in equation (5), the cleavage taking place because of the stability of the tertiary carbonium ion.

$$R_3C\,(:)\,C(OH)_2 \;\rightarrow\; H\text{-}\overset{\oplus}{N}\text{-}N{\equiv}N: \;\rightarrow\; R_3C^{\oplus} + N_2 + \left[\begin{matrix} C(OH)_2 \\ H\text{-}N \\ \cdot\cdot \end{matrix}\right] \rightarrow CO_2 + NH_3 \qquad (5)$$

A similar cleavage was observed by Smith (12) with pivalophenone.

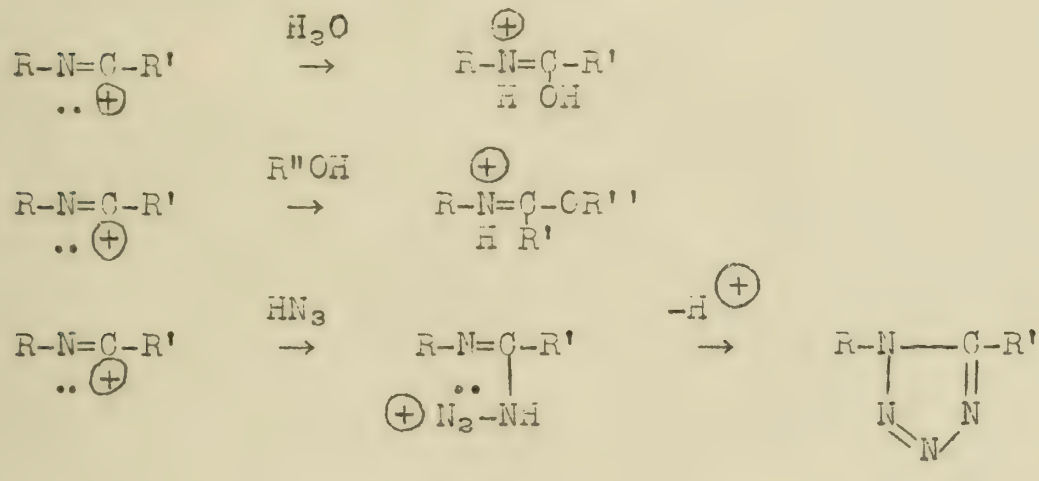
Interesting verification of the mechanism is provided by the reaction with ketones. If the addition of hydrazoic acid to $R_2\overset{\oplus}{C}$-OH is the rate determining step, the rate should be proportional to the concentration of $R_2\overset{\oplus}{C}$-OH and, therefore, roughly proportional to the basicity of the ketone and acidity of the solvent. In accordance with this, Smith (9) has observed that only the more basic aliphatic ketones react in such basic solvents as water, alcohols and ethers, and more acidic catalysts are necessary for the less basic ketones. Concentrated aqueous hydrochloric acid is a sufficiently acidic catalyst and solvent for aliphatic ketones, trichloroacetic acid being necessary for aralkyl ketones, and sulphuric acid for diaryl ketones and carboxylic acids. With the intermediates shown in equation (2) the rules for migration of the groups in unsymmetrical ketones should be those for migration in symmetrical pinacols (10), that is, the groups with greater electron release should migrate preferentially. This has been found to be the case in the compounds tested. Thus, for example, aryl > alkyl, Et > Me, p-Me-Ø > Ø (11).

However, the reaction may be considered as analogous to the Beckmann Rearrangement (9,12), in which case steric factors will govern the migration where similar electrical effects are involved.



I II III

The intermediate III is the same as that in the Beckmann Rearrangement, and it undergoes various reactions according to its nature and the other species present.



(7)

(8)

(9)

(10)

These products are formed in both the Beckmann and Schmidt reactions. The more bulky R group should migrate, because of steric effects, but unfortunately both criteria for migration lead to the same results in the compounds tested so far, and no unequivocal conclusion can be reached.

The carbonium ion mechanism seems to be fairly well established and there is strong evidence for the Beckmann type of rearrangement.

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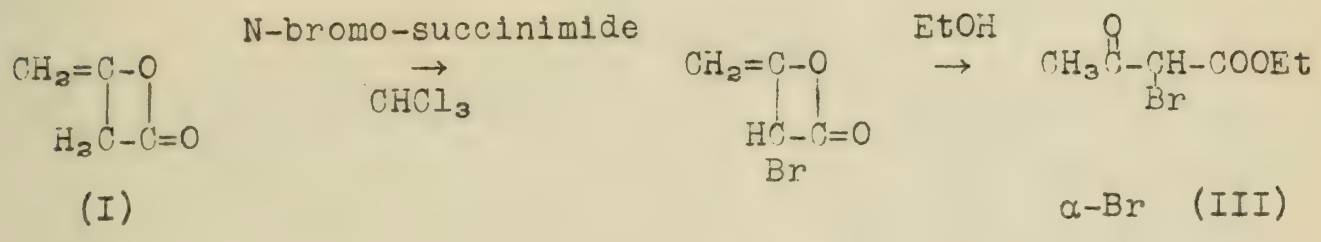
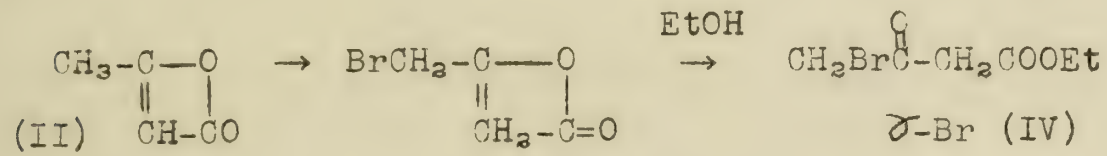
Reported by Elizabeth J. Underhill
March 19, 1948

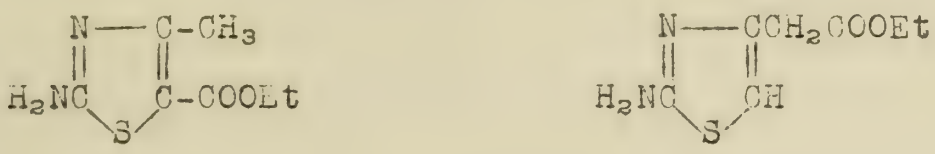
A NEW SYNTHESIS OF MANY MEMBERED CARBON-RINGS

Consideration of the most reliable evidence to date indicates structure I and II as being the most likely ones for ketene dimer (2). Ziegler's reagent for halogenation at allyl positions should distinguish between these two. The reactions are shown in the following:





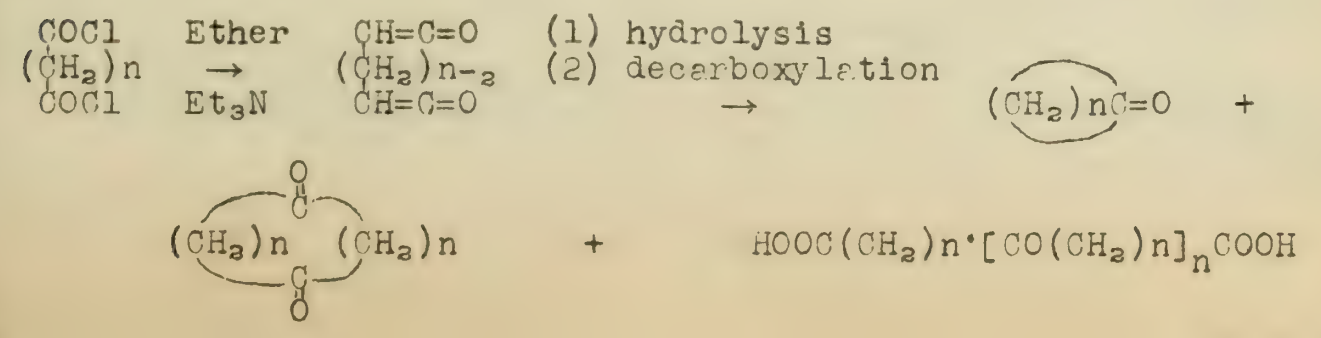
The resulting haloacetoacetic ester was characterized by conversion to the known solid derivative by treatment with thiourea. The reaction gave compound V and none of compound (VI). It is significant that there was no evidence for the presence of γ-haloacetoacetic ester in the reaction product.



(V) (VI)

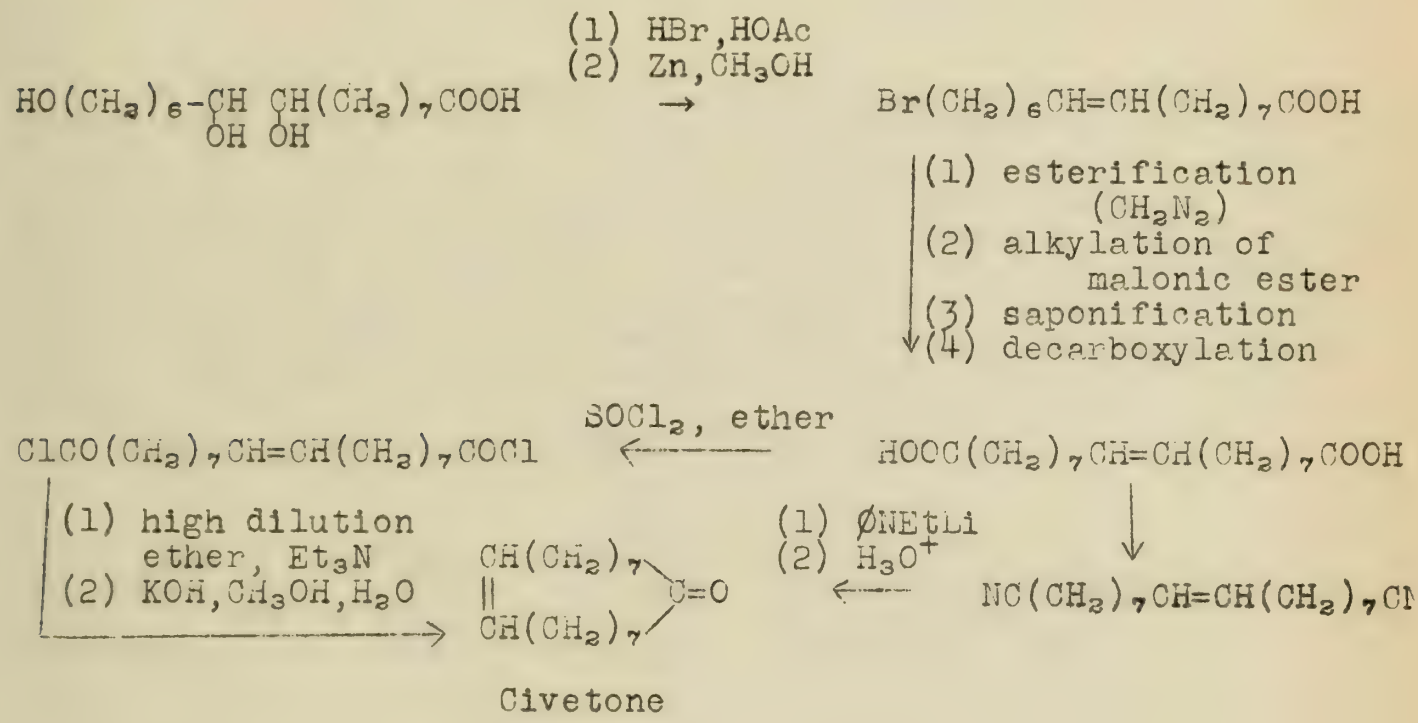
Sauer (10) in preparing ketene dimers from acid halides observed that the bifunctional ketene derived from adipyl chloride gave a 40% yield of α-carbethoxycyclopentanone, when treated with ethyl alcohol, while that from sebacylchloride yielded only a polymeric ketene with no evidence of the formation of a cyclic compound.

The products obtained by dimerization of biketene under extreme dilution (6,9) are shown below:

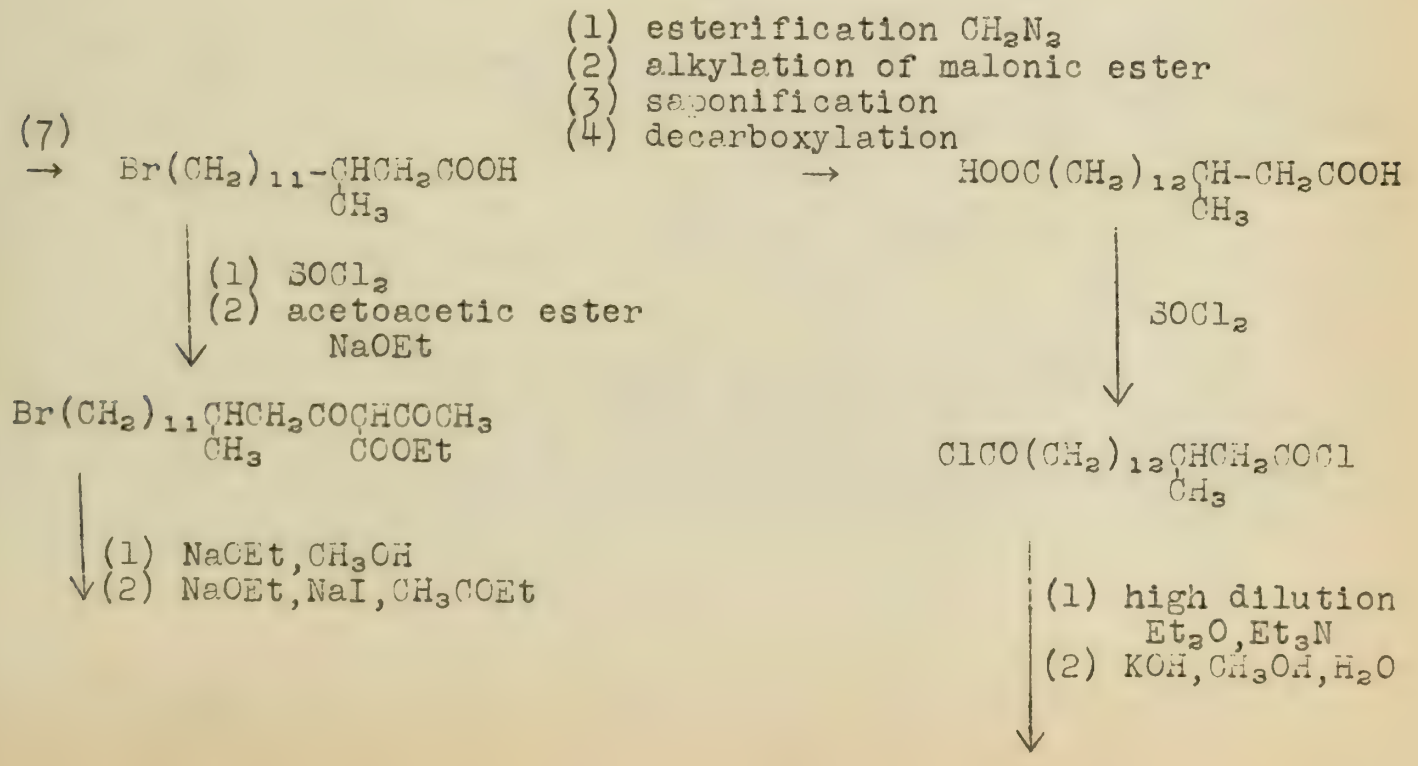


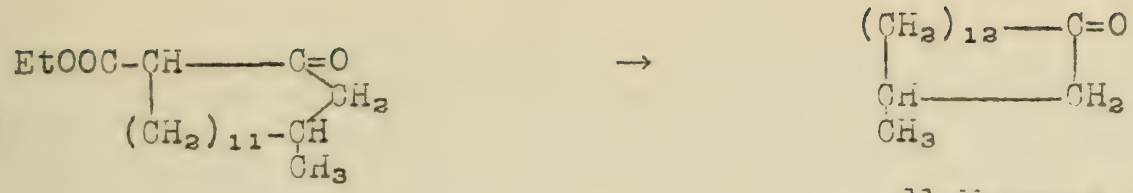
The polymeric material is easily separated from the cyclic material (3). Of the three tertiary amines, N-ethyl piperidine, tributylamine and triethyl amine, tested the last resulted in the best yield.

Synthesis of Civetone (1,3,8,9),



Synthesis of dl-Muscone,

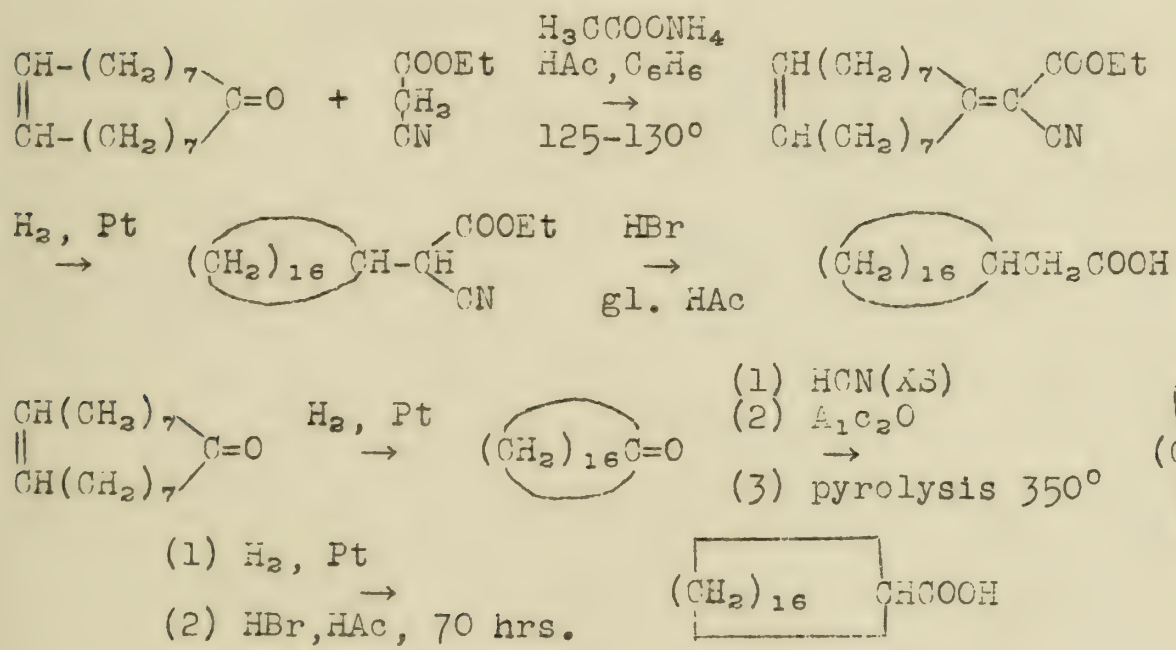




dl-Muscone

The yield of civetone and dl-muscone by the cyclization of bifunctional ketene are superior to those obtained by Ruzicka, but inferior to those of Hunsdiecker. However, the ease of synthesis of necessary intermediates and the ease of separating the cyclic ketones from the accompanying by-products, make the ketene-method far better than the other two. Due to the possible therapeutic value Blomquist and Holley (4) undertook an investigation of the properties of many-membered carbon rings containing the carboxyl group. They have prepared two types of large ring carboxylic acid,

$(CH_2)_n\,CHCOOH$ and $(CH_2)_n\,CHCH_2COOH$.



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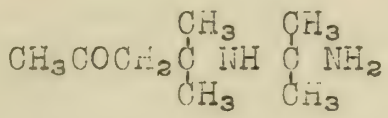
Reported by Elizabeth H. H. Shen
April 2, 1948

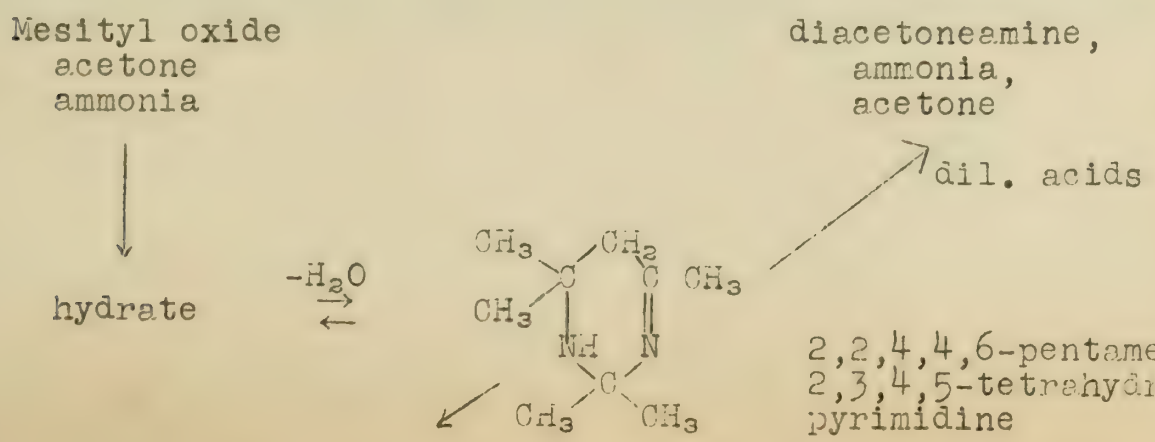
A NEW PRODUCT FROM THE REACTION OF ACETONE AND AMMONIA

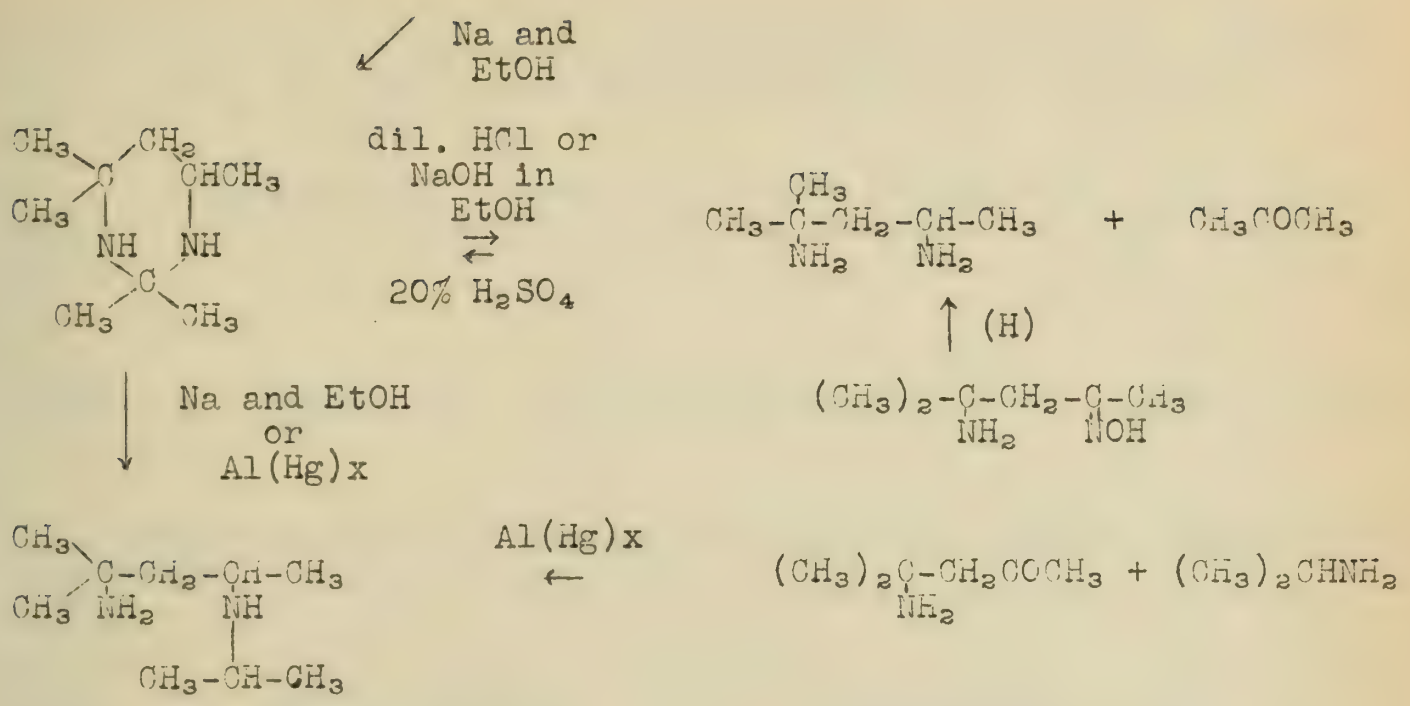
In view of the behavior of formaldehyde and acetaldehyde toward ammonia, Franklin (1) has suggested that one might expect to find among the reaction products of acetone and ammonia compounds of one or more of the following types: $(CH_3)_2C(OH)NH_2$, $(CH_3)_2C(NH_2)_2$, $(CH_3)_2C{=}NH$, $[(CH_3)_2C{=}NH]_3$, $[(CH_3)_2C{=}N]_2C(CH_3)_2$, and $[(CH_3)_2C]_6N_4$. None of these products has been obtained, with the possible exception of a compound isolated by Hoch and Stuhlman (2) whose properties would indicate the first type. However, three definitely characterized products of the reaction of acetone and ammonia have been known for many years. These are diacetoneamine, triacetoneamine, and triacetonediamine.

Moreover, several investigators (3,4,5) have reported a compound of the empirical formula $C_9H_{18}N_2$ whose structure they failed to elucidate. This substance was called "acetonin". It was thought that in at least one case the material in hand was only impure diacetoneamine. In 1921, Patterson and McMillan (6) found an unexpected crystalline substance in the reaction mixture from which they usually obtained diacetoneamine. This compound had the formula $C_9H_{20}N_2O$ and they proposed the structure



Last year, almost simultaneously, Matter (7) at the University of Basel, and a group of Australians, Bradbury, Hancox, and Hatt (8), described the preparation and proof of structure of a compound with the formula $C_9H_{18}N_2$ from the reaction of acetone and ammonia. This substance, which Matter called acetonin, readily formed a hydrate, $C_9H_{20}N_2O$, identical with the compound of Patterson and McMillan. It was obtained by using a mixture of calcium chloride and ammonium chloride as catalyst. The new base is a colorless liquid, which rapidly turns yellow, possesses an ammoniacal odor, and is readily soluble in water and the common organic reagents. That it is 2,2,4,4,6-pentamethyl-2,3,4,5-tetrahydropyrimidine is proven by the following reactions:





The preparation of diacetoneamine oxalate through "acetonin" can be accomplished in an overall yield of 56% based upon the acetone used, which compares favorably with the present method in yield and is more convenient. Acid hydrolysis yielding 2,4-diamino-2-methyl pentane can be accomplished in yields of 80% with less trouble than by reduction of the corresponding oxime.

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Reported by Eric Barthel
April 2, 1948

THE CHEMISTRY OF THE NITROGEN MUSTARDS

The chemistry of the nitrogen mustards, a group of vesicant chemical warfare agents, received much attention during the recent war. These substances are β-chloroethylamines of the general formula, $R\text{-}N(CH_2CH_2Cl)_2$.

I. Preparations.--They are usually prepared from the corresponding alkyl diethanol amines by the action of thionyl chloride (2).

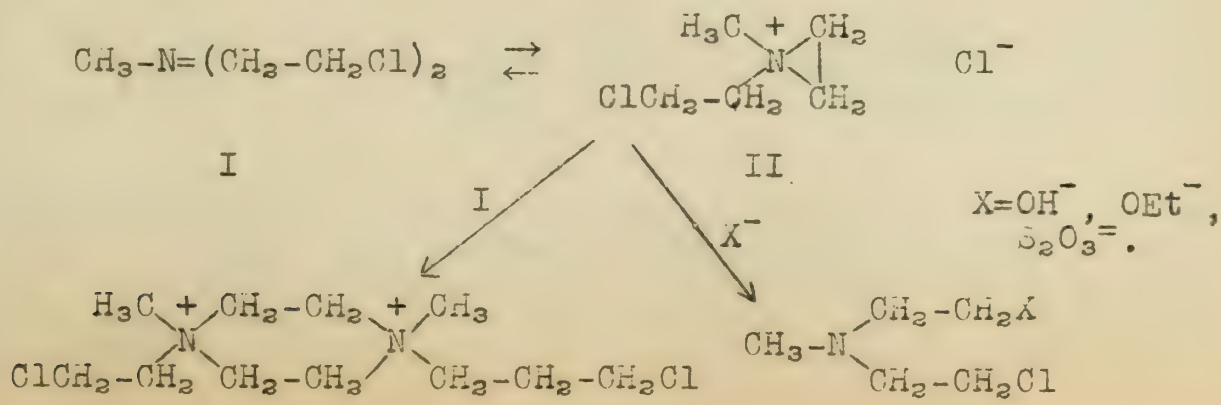
$$R\text{-}NH_2 + \underset{\diagdown O \diagup}{CH_2\text{-}CH_2} \rightarrow R\text{-}N{=}(CH_2\text{-}CH_2OH)_2 \xrightarrow{SOCl_2} R\text{-}N{=}(CH_2\text{-}CH_2Cl)_2$$

Methyl diethanol amine may be better prepared according to the equation:

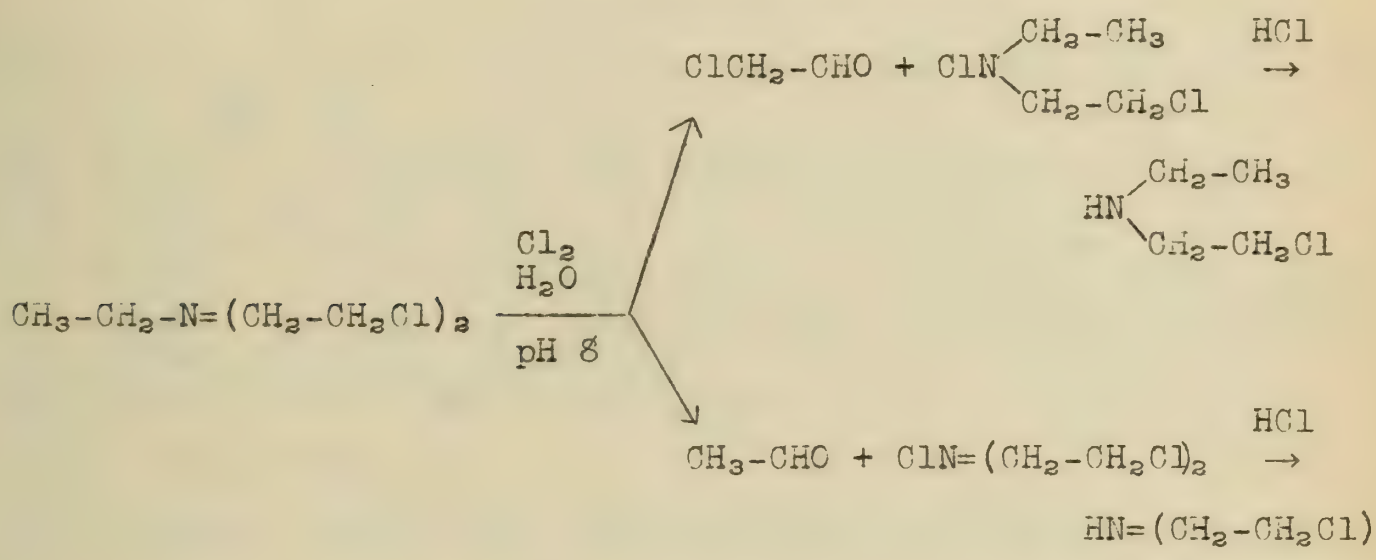
$$HCHO + HN{=}(CH_2\text{-}CH_2OH)_2 \xrightarrow{HCO_2H} CH_3\text{-}N{=}(CH_2\text{-}CH_2OH)_2$$

II. Properties.--The nitrogen mustards are unstable and will deposit a solid dimer if allowed to stand at room temperature. While this dimerization is slow for the pure, anhydrous amine, it is very rapid in methanol solution (explosive, in the case of methyl bis-β-chloroethylamine, if large enough quantities are used). These dimers exist in a cis and a trans form. In the case of the methyl analog they are easily separable and the high melting, less soluble form has been shown by x-ray analysis to have the trans configuration (1).

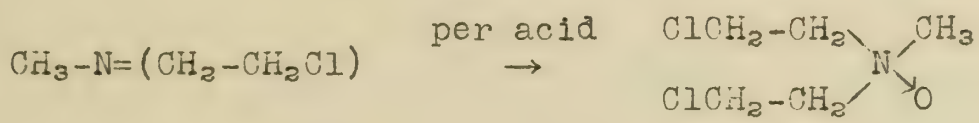
III. Reactions in Aqueous Solution.--The behavior of these amines in aqueous solution has been studied extensively because of their possible use as chemical warfare agents (against biological systems and to contaminate water sources) (2,3,4,5,6,8,9,10,11,16). Hydrolysis and dimerization are competing reactions. They have been found to proceed through a common, rate determining step, the formation of the ethyleneimmonium ion. The reactions may be represented thusly:



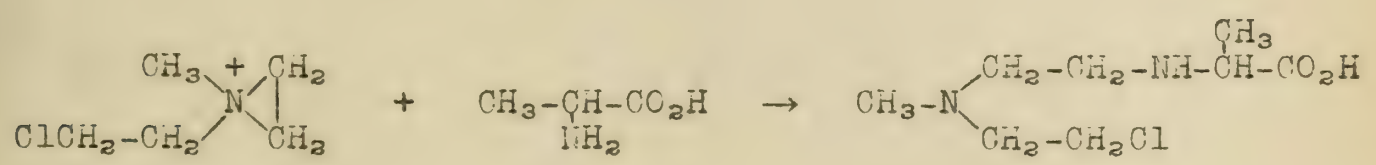
IV. Chlorination.--The nitrogen mustards are cleaved by treatment with aqueous hypochlorite solution to an aldehyde and bis-β-chloroethylchloramine, or to chloroacetaldehyde and an alkyl-β-chloroethylchloramine. The former products predominate in the case of methyl bis-β-chloroethylamine but the reverse is true for the ethyl analog (16).



V. Oxidation.--The oxidation of the nitrogen mustards to the corresponding amine oxides by per acids competes favorable with hydrolysis (15). The amine oxides have been obtained in 78-85% yields in the form of their hydrochlorides (16).



VI. Reactions with Compounds of Biological Interest.--The nitrogen mustards in aqueous solution react in vitro with free amino, free carboxyl, sulfide, and imidazole groups in amino acids and proteins. Here too the reactive agent is the ethyleneimmonium ion (12).



The amine group seems to be attacked in preference to the carboxyl group and the free amino group of a dipeptide is more reactive than one of an amino acid. Competitive reactions, using alanine as a standard, have shown that the ease of attack by methyl bis-β-chloroethylamine decreases in the following order: pyridine,

nicotinic acid, thiamine, imidazole, glucose-6-phosphate, pyridoxine, l-alanine, carbobenzoxy l-glutamic acid (13).

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Reported by H. V. Anderson
April 2, 1948

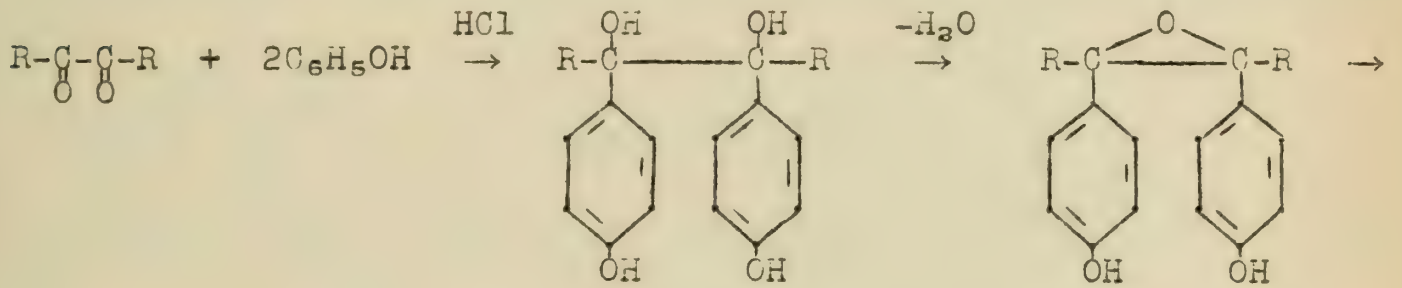
REACTIONS OF KETONES WITH PHENOLS

Although aldehydes and phenols react to form polymers, the reaction of ketones and phenols in the presence of acid catalysts yields compounds which exhibit none of the characteristics of polymers. Two general types of compounds are formed: (1) direct condensation products and (2) oxygen heterocyclic compounds.

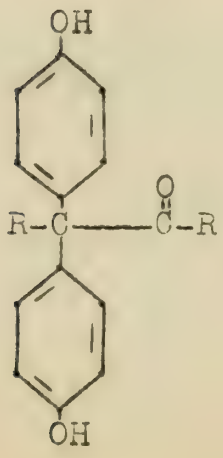
In the simple condensation reactions the ketone and the phenol combine to form the intermediate "phenol-hydrin" molecule (I); then another molecule of phenol adds with the elimination of water. The phenol always reacts in the para position unless it is blocked. The reaction is carried out in the presence of dry hydrogen chloride. These substance have found industrial uses.

I II

Gamma diketones react similarly to yield the tetrasubstituted product. However, α,β-diketones react with only two molecules of phenol. This fact is explained as follows:

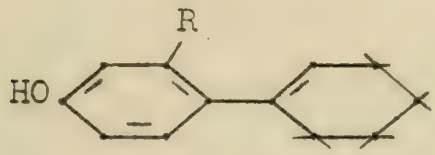


III IV

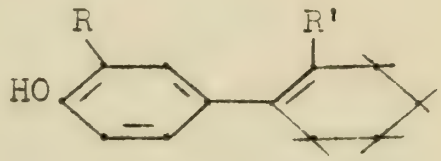


V

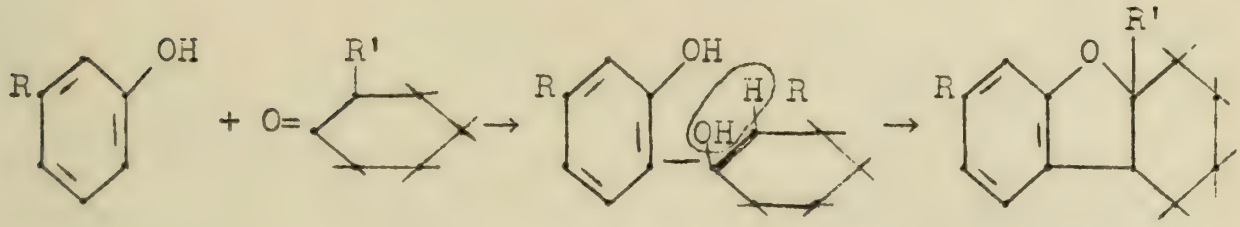
In cases where either the phenol or the ketone offers steric hindrance, only one phenol reacts. Thus, if a meta alkyl phenol is reacted with cyclohexanone, the product is of the type of structure (VI). When an ortho alkyl phenol and a 2-alkylcyclohexanone are reacted, the product is of the type of structure (VII). If both reactants are hindered, the product is a coumaran (IX).



VI

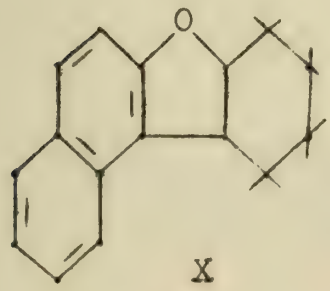


VII

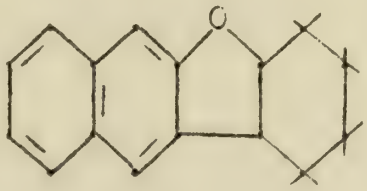


VIII IX

A coumaran is also the product when β-naphthol is reacted with cyclohexanone. Its structure is thought to be either (X) of (XI).

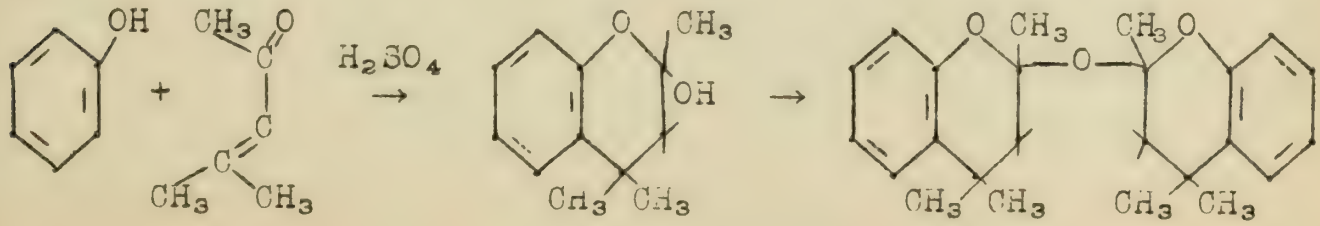


X



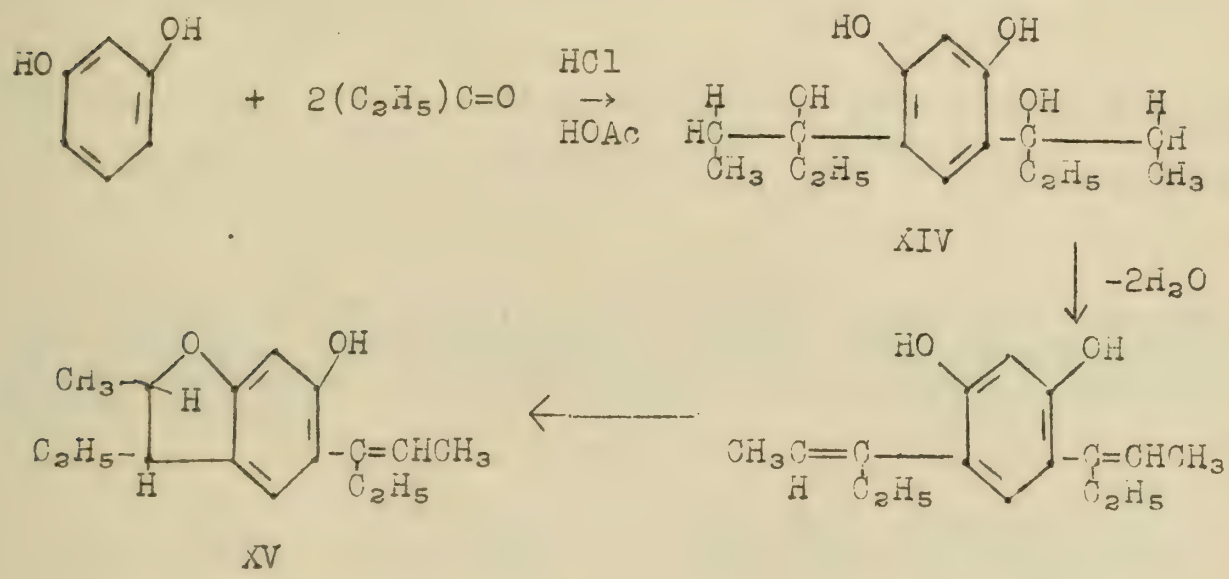
XI

Mesityl oxide and phenol in the presence of sulfuric acid form a chromanol (XII) which condenses with itself to form a dicromanyl ether (XIII).



XII XIII

When the reaction is extended to polyhydric phenols, the results are more complicated. Oxygen heterocyclic compounds are the usual products. An example is the condensation of resorcinol in the presence of dry hydrogen chloride and acetic acid with two molecules of diethyl ketone. The intermediate (XIV) which loses two molecules of water cyclizes to give the product of structure (XV).



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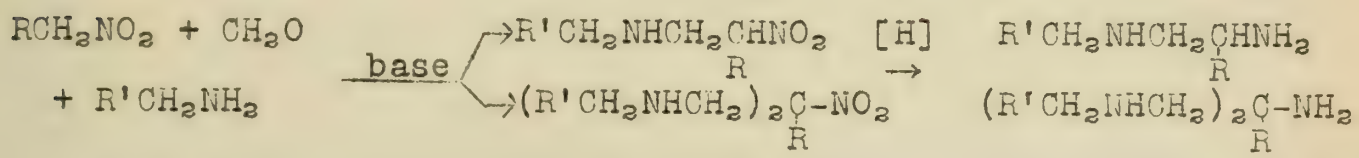
Reported by Joseph R. Gordon
April 2, 1948

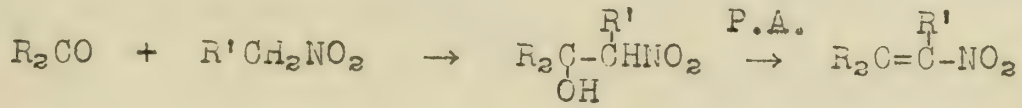
REACTIONS OF SATURATED NITRO COMPOUNDS

Due to the recent availability of aliphatic nitro compounds, studies of their reactions have been extensive (1-6).

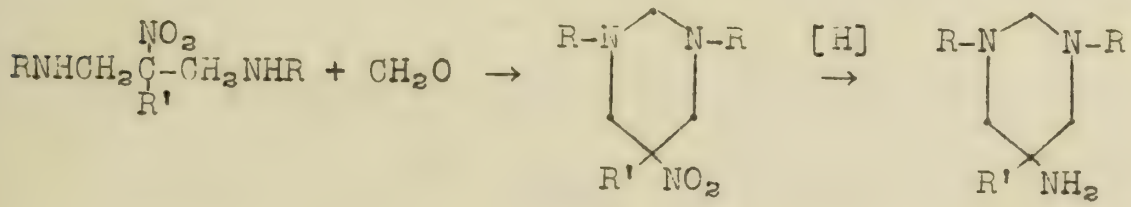
Nitroparaffins react with formaldehyde and aliphatic or aromatic amines to give good yields of nitroamines. Primary or secondary amines and primary or secondary nitroparaffins may be used. The resulting nitroamines may be catalytically reduced to di- or polyamines (7-11).



Primary nitroparaffins react with aliphatic or aromatic carbonyl compounds to yield nitroalcohols. These alcohols may be easily dehydrated to nitro-olefins by heating with phthalic anhydride (12-19).

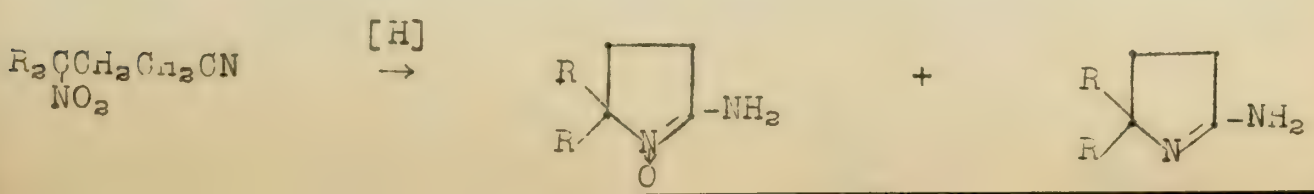


2-Nitro-1,3-propanediamines react with formaldehyde to give 5-nitrohexahydropyrimidines. These compounds may be catalytically reduced to the corresponding 5-amino compounds (20).

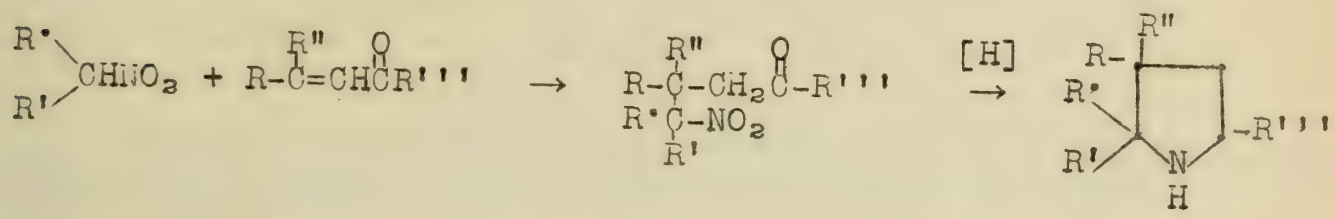


Catalytic reduction of 2-nitroalkylcyanides gave very poor yields of the expected 2-amino compounds. Instead, hexahydropyrimidines and 2-aminoalkylamides were obtained. The mechanism of cyclization is unknown (21).

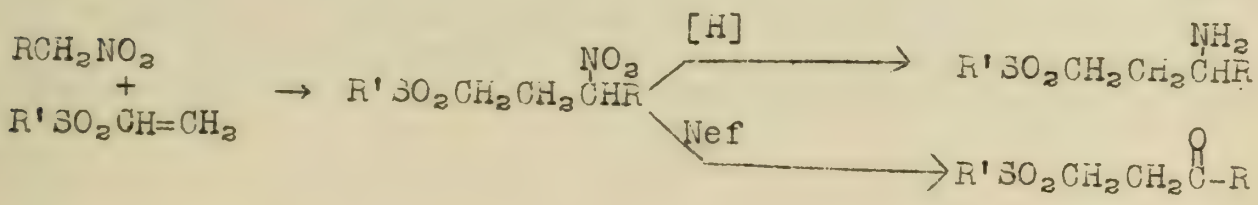
Chemical or catalytic reduction of 3-nitroalkylcyanides leads to good yields of substituted pyrrolines and pyrroline-N-oxides (22, 23).



When a primary or secondary nitroparaffin is reacted with an unsaturated ketone in the presence of base, a Michael addition occurs yielding a γ-nitroketone. These nitroketones, on catalytic reduction over nickel, cyclize to substituted pyrrolidines (24).



In a like manner, the nitroparaffins add to unsaturated sulfones to give 3-nitroalkylsulfones. These may be reduced to the corresponding amino compounds or converted to ketosulfones by the Nef Reaction (25).



Most of the nitroparaffins are easily reduced to the corresponding amino compounds by hydrogen and Raney nickel catalyst (26). Certain nitro compounds (mentioned above) give heterocyclic bases when reduction is attempted. Low molecular weight nitro compounds undergo electrolytic oxidation and reduction in basic solution (27).

cathode reaction: $RNO_2 + 4H \xrightarrow{+e} RNHOH + H_2O$

possible anode reactions:

(a) $R_2CNO_2^- \xrightarrow{-e} R_2\dot{C}NO_2 \rightarrow R_2C(NO_2)-C(NO_2)-R_2$

(b) $R_2CNO_2^- \xrightarrow{-e} R_2\dot{C}NO_2 \rightarrow R_2CO + NO$

(c) $R_2CHNHOH \xrightarrow{-e} R_2CHN{=}O \rightarrow R_2C{=}NOH$

Esters of nitroalcohols, $R\overset{O}{\overset{\|}{C}}-OCH_2CH_2NO_2$, other than the formic ester, are prepared in the usual way. The formic esters may be prepared by treatment of the nitroalcohol with formic-acetic anhydride (28).

The heterocyclic base, gramine, may be used to alkylate nitro compounds in the presence of a base. The product may be mono- or

dialkylated (29).

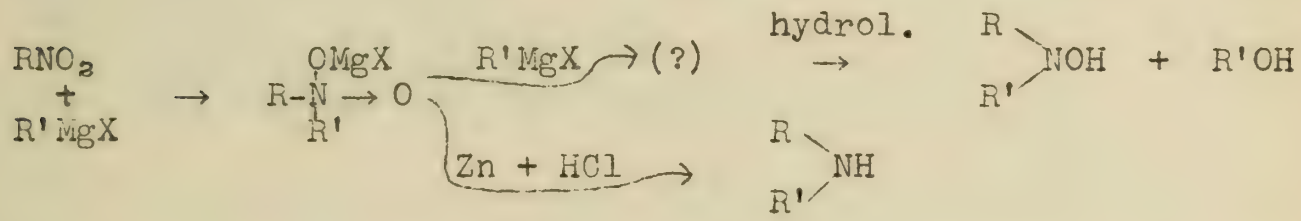
The low molecular weight nitro compounds give good yields of the corresponding carbonyl compounds by the Nef Reaction (30).

$$R_2CHNO_2 \xrightarrow{\text{base}} R_2C{=}NO_2Na \xrightarrow{\text{mineral acid}} R_2C{=}O + N_2O$$

Diazonium salts couple with nitroalkanes in cold, basic solution to give more or less stable compounds of the type, $ArN{=}N{-}\underset{R}{CH}{-}NO_2$ (31).

Nitroalkanes add to nitro-olefins in the presence of base to give 1,3-dinitroalkanes (32).

Nitrocompounds react with Grignard reagents in two steps. First, RMgX adds to the -N=O group to form a complex. The complex is reduced by a second mole of RMgX by an unknown mechanism to a product which on hydrolysis yields a dialkylhydroxylamine. If the complex is reduced by zinc and hydrochloric acid, a dialkylamine results (33).



Only one radically different type of reaction was reported in the patent literature. Primary nitro compounds, refluxed with constant boiling hydrochloric acid, give the corresponding acid and hydroxylamine hydrochloride (34).

$$RCH_2NO_2 + HCl \xrightarrow{\Delta} RCOOH + H_2NOH{\cdot}HCl$$

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Reported by John P. Pellegrini
April 9, 1948

POLYURETHANS

Introduction.--Two general methods for preparing high molecular weight compounds, namely condensation polymerization and addition polymerization, are known. Both have their respective merits and disadvantages. For example, condensation reactions (the formation of Nylon is typical) are favorable in that they permit flexibility of composition and also allow linkages of hetero atoms to exist; they are disadvantageous in that as a rule very vigorous conditions must be employed, and in that a small molecule, such as water, is eliminated during the reaction and must either be removed or allowed to remain in the resultant polymer. On the other hand, addition polymerization proceeds under mild conditions with no elimination of small products; however, in practice, only carbon to carbon linkages are formed, and usually only the end products are obtainable. The formation of polyurethans combines the possibilities and advantages of condensation and of addition polymerization methods and proceeds under mild conditions by purely additive reactions to a (controllable) variety of end products.

Work on polyurethans was started by German chemists shortly after the publication of Carothers' work on polyamides, in an effort to synthesize products as good as or better than Nylon, but not covered by duPont patents. Wurtz, over a hundred years ago, found that an isocyanate adds smoothly to an alcohol to form a urethan, the hydrogen atom of the hydroxyl group being displaced to the nitrogen atom of the isocyanate group, without the liberation of any small product.

$$RNCO + HOR' \rightarrow R-\overset{H}{N}-\overset{O}{\overset{\|}{C}}-OR'$$

Polyurethans are formed in an analogous manner from diisocyanates and poly-hydroxy compounds.

Linear Polyurethans.--The most useful and fortunately the most easily manufactured polyurethan is prepared from 1,6-hexanediisocyanate and 1,4-butylene glycol.

$$-NCO + HO(CH_2)_4OH + OCN(CH_2)_6NCO + HO(CH_2)_4OH + OCN-$$

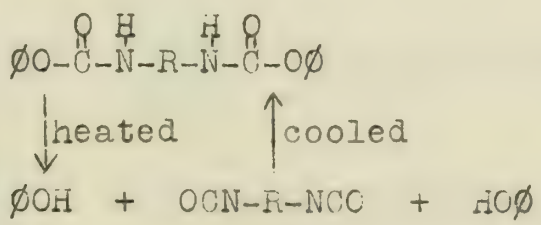
$$\downarrow$$

$$-\overset{H}{N}-\overset{O}{\overset{\|}{C}}-O-(CH_2)_4-O-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-(CH_2)_6-\overset{H}{N}-\overset{O}{\overset{\|}{C}}-O-(CH_2)_4-O-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-$$

Formally, this structure differs from Nylon 66 only in that there are two additional oxygen atoms in each recurring unit. It is obvious that simply by varying the number of monomer methylene groups there is possible a large number of different linear polyurethans, and many of these have been prepared. However, we shall limit our consideration to the example, Perlon U, given above, and

will compare it in some respects with the corresponding superpolyamide (Nylon). Perlon U is prepared by the addition of the diisocyanate to the glycol, either molten or in chlorobenzene, and is suitable for the manufacture of artificial silk fabrics and especially, because of its low affinity for water, of bristles. It shows a high degree of homogeneity of molecular weight distribution and has a sharp melting point. Like the superpolyamides, its properties as a fiber are improved by stretching, and X-ray patterns indicate a very high degree of crystallinity in the resultant filaments. Perlon U has a tensile strength about equal to that of Nylon and is superior to it in electrical properties, stability to weathering, resistance to acids, retention of dimensions, and above all, as mentioned above, in resistance to water; also, having no basic groups, it can be dyed with non-acidic dyes such as those used with acetate silks. Its chief disadvantage is its lower melting point, about 185°, which is about the same as that of acetate rayon. The Germans claim that for them Perlon U is no more expensive than Nylon to make, and will eventually be even cheaper.

Cross-linked Polyurethans.--The linear polyurethans are all thermoplastic and are soluble in some organic solvents. If, however, diisocyanates are reacted with compounds having more than two reactive hydrogen atoms, e.g. with glycerol, cellulose acetate, etc., three-dimensional insoluble and infusible macro-molecules are obtained. Many of these products are excellent lacquers, but are so insoluble that trouble is encountered in applying them to surfaces. One method for surmounting this difficulty is the use of a double-jet nozzle, spraying isocyanate and hydroxy compound separately but simultaneously, the reaction taking place on the surface itself. A somewhat more interesting scheme from the chemical point of view consists in the so-called 'masked isocyanate' method; to the polyhydroxy compound is added, instead of a diisocyanate, a compound which when heated reacts like an isocyanate. For example, bisphenylurethan, obtained either from a diisocyanate and phenol or from phenylchloroformic acid and a diamine, reacts:



The mixture can thus be applied directly to the surface and on heating, the diisocyanate is formed, and then the cross-linked polyurethan, the phenol being evaporated. By variation of either monomer many other useful resinous products can be synthesized, among them a substance much like Bakelite, except that it is very elastic (shown by impact bending strength).

Miscellaneous Reactions and Uses.--By treating diisocyanates

with polyesters containing both free hydroxyl and carboxyl groups, very strong and lightweight substitutes for balsa wood were made, the so-called expanded or 'solid-foam' materials. Along with urethan formation, the following type reaction occurs:

$$R\text{-}COOH + OCN\text{-}R' \rightarrow R\text{-}\overset{O}{\overset{\|}{C}}\text{-}\overset{H}{\overset{|}{N}}\text{-}R' + CO_2$$

Thus a polyurethan-polyamide compound is formed, along with carbon dioxide, the latter blowing the product up like dough into a light and strong honeycomb-like material.

Another potentially important use of diisocyanates is in the vulcanization of rubber to give a product which adheres tenaciously to metal surfaces. The mechanism of the vulcanization is uncertain, but diisocyanates will definitely add to Buna-S, and the rubber thus formed will adhere to metals, porcelain, etc. A possible mechanism for the adherance is postulated: diisocyanates react even with hydrated oxide layers on the metal surface, so producing a clean surface wherein the urea groups of the adhesive most probably form chemical bonds, or at least subsidiery valency bonds, with the residual valencies of the metal lattice.

Preparation of Monomers.--The diisocyanates are called Desmodurs and are made from aromatic diamines or aliphatic diamine salts and phosgene. The preparation of the isocyanate for Perlon U involves, incidently, the total synthesis of hexamethylene diamine from acetylene, HCN, and formaldehyde:

$$HC{\equiv}CH + 2\ CH_2O \xrightarrow{\text{Reppe}} HOCH_2C{\equiv}CCH_2OH \qquad (a)$$

$$HOCH_2C{\equiv}CCH_2OH \xrightarrow{\text{Raney Fe}} HOCH_2CH{=}CHCH_2OH \qquad (b)$$

$$HCN + HOCH_2CH{=}CHCH_2OH \xrightarrow[NH_4Cl]{CuCl} CNCH_2CH{=}CHCH_2CN \qquad (c)$$

$$CNCH_2CH{=}CHCH_2CN \xrightarrow[\text{cat.}]{[H]} NH_2CH_2CH_2CH_2CH_2CH_2CH_2NH_2 \qquad (d)$$

$$NH_2(CH_2)_6NH_2 + 2\ COCl_2 \xrightarrow{-2\ HCl} [O{=}\underset{Cl}{C}\text{—}\underset{H}{N}\text{-}(CH_2)_6\text{-}\underset{H}{N}\text{-}\underset{Cl}{C}{=}O] \qquad (e)$$

$$\downarrow -2HCl$$

$$OCN\text{-}(CH_2)_6\text{-}NCO$$

Many of the polyhydroxy compounds are made by means of the Reppe synthesis. For Perlon U, the 1,4-butanediol (an intermediate in the synthesis of butadiene) is obtained by catalytic hydrogenation of the product of reaction (a) above.

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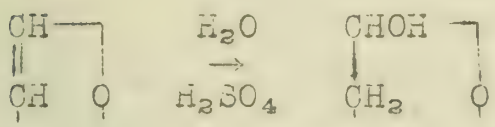
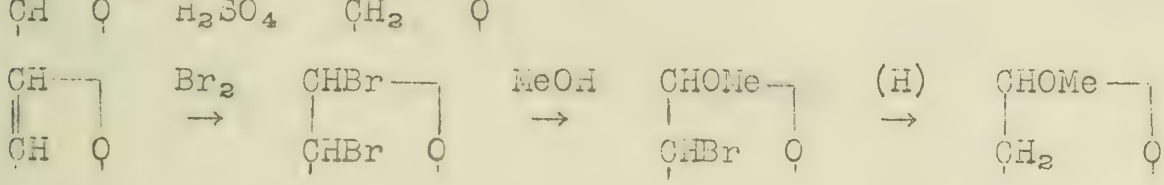
Reported by D. J. Shields
April 9, 1948

A NEW SYNTHESIS OF DESOXY SUGARS

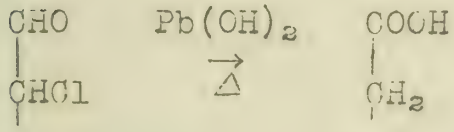
Desoxy sugars are carbohydrates that have one or more CHOH groups replaced by a CH_2 group. Previous preparations of 2-desoxy sugars were by hydration of a glycal (I), reduction of the methylation product from the bromination of a glycal (II), heating of a 2-chloro-sugar with lead hydroxide to a desoxy-hexonic acid (III), and by catalytic reduction of a nitro-olefin followed by hydrolysis (IV). A 3-desoxy sugar has been prepared by hydrogenation of a glycoseen. However, these syntheses sometimes give low yields or none at all.



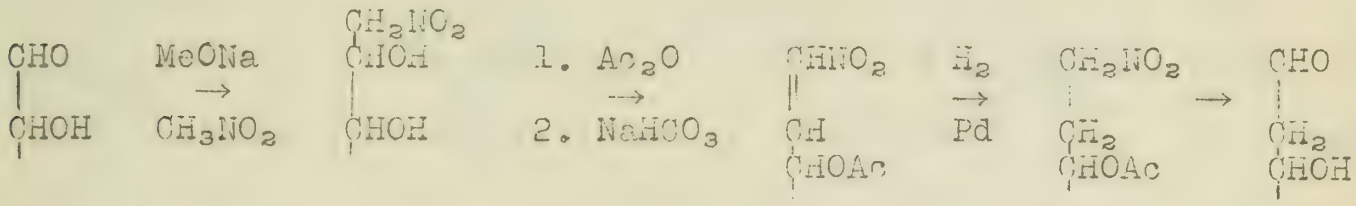
(I)



(II)

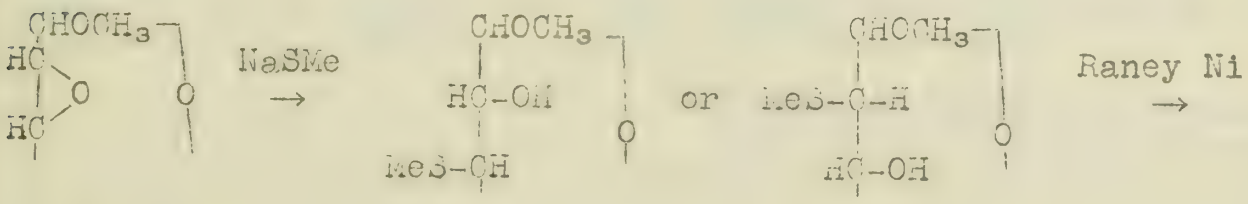


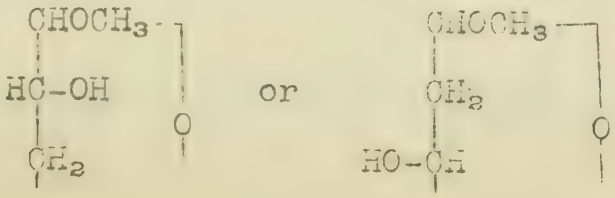
(III)



(IV)

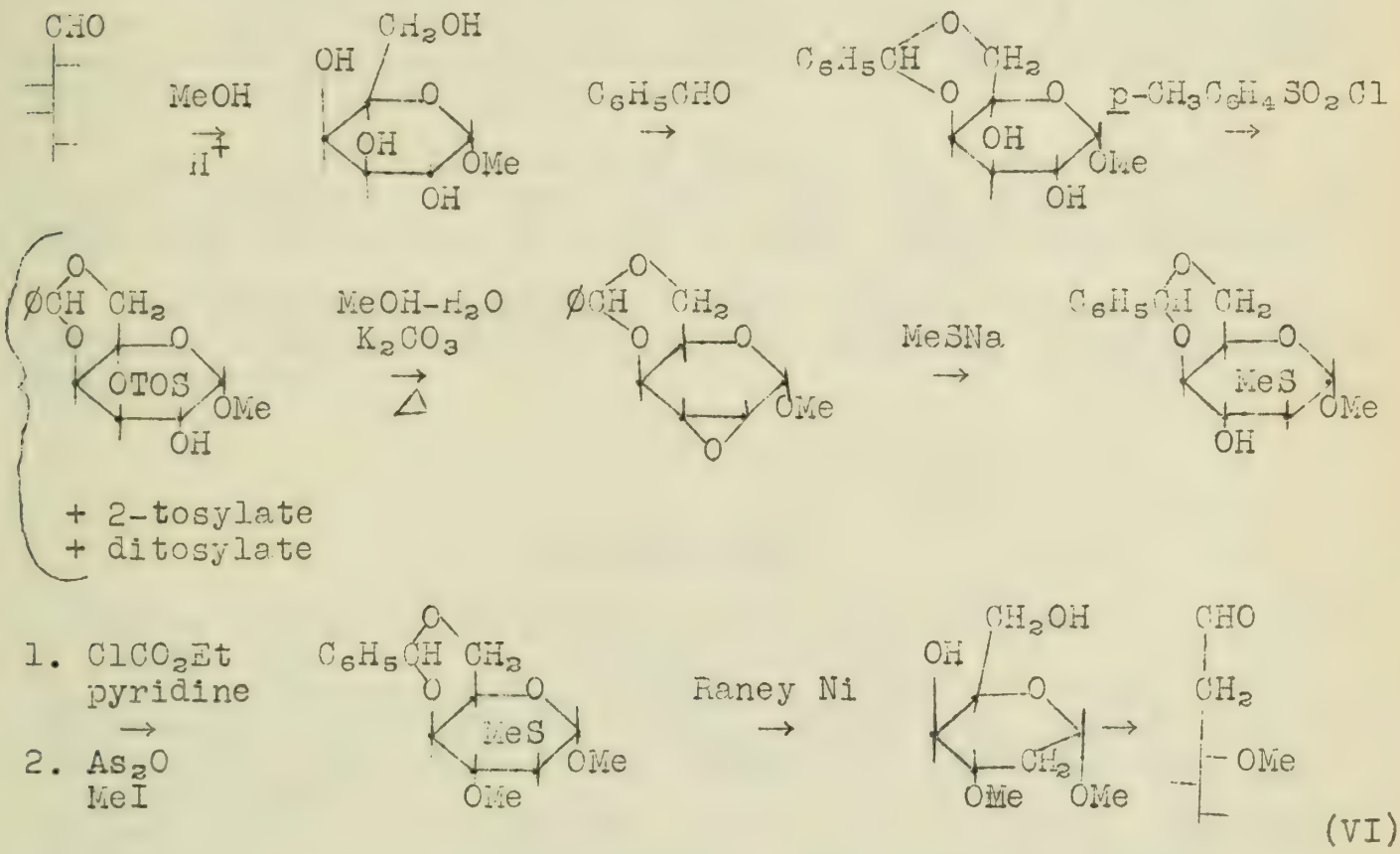
New Synthesis.--Gut, Prins, and Reichstein developed a method of greater applicability than the preceding ones based on work by Robertson and Griffith and Mozingo, Wolf, Harris and Folkers. The addition of NaSMe to a 2,3-anhydro sugar yields either a 2- or 3-methylmercapto sugar which can be reduced by Raney Ni to the 2- or 3-desoxy sugar (V).





(V)

The problem in this method, as in all carbohydrate reactions, is to prepare the proper anhydro intermediate, which is done by protecting other reactive groups. The preparation of 2-desoxy-d-gulose 3-methyl ether from galactose is shown (VI):



(VI)

The anhydro sugar is usually prepared from the p-toluenesulfonyl (tosyl) derivative, which reacts with a trans -OH to form an epoxy ring trans to the original tosyl-derivative, by a Walden inversion.

Rule of Splitting the Ethylene Oxide Ring.--The ethylene oxide ring of 4,6-benzal-2,3-anhydro-α-methylhexosides reacts with both NaOMe and NaSMe in the same way: in the d-series, the -SMe or -OMe group enters the 2-position when the epoxy ring is to the right in a Fischer projection and enters the 3-position when it is to the left; in the l-series, the group enters the 2-position if the ring is to the left and the 3-position if to the right.

This rule applies also to a β-methyl hexoside, 2,3-anhydro-4,6-benzal-β-methyl-d-taloside. But neither the α- nor the β-methyl-l-ribopyranoside derivative formed the 2-desoxy compound, only the 3-desoxy one, which may be due to the lack of asymmetry on the 5-carbon.

Reaction Technique.--The anhydro-sugar is converted by refluxing with Na, MeSH, and MeOH to the methylmercapto-derivative, which is reduced by heating with Raney Ni in alcohol and water, no gaseous hydrogen being necessary. Desoxy sugars which have

been prepared this way are 3-desoxy-l-xylose, 3-desoxy-d-idose 2-methyl ether, 3-desoxy-d-mannose, 2-desoxy-d-gulose 3-methyl ether, 2-desoxy-d-allose, and its 3-methyl ether.

Methods of Structure Proof.--Oxidation of these compounds to acids and conversion to the diamide is used to prove the identity of the original compound. For example, 3-desoxy-d-idose 2-methyl ether yields l(-)-methoxysuccinamide, while the 2-desoxy-d-idose would give the d-methoxysuccinamide.

The Keller-Kiliani test is specific for 2-desoxy sugars; a blue or green color is given when a few drops sulfuric acid, containing 5% ferric ion, is added to their acetic acid solution.

The structure of synthetic desoxy sugars can be proven by identity with the naturally occurring products, ex: d-digitoxase and d-cymarose.

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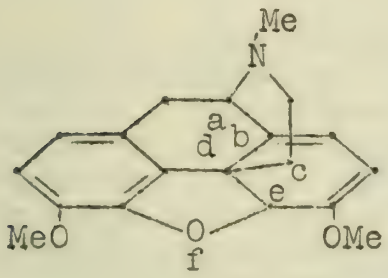
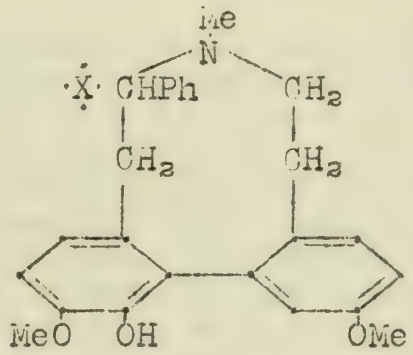
Reported by Bernard R. Bluestein
April 9, 1948

REACTION OF THEBAINE WITH PHENYLMAGNESIUM BROMIDE

In 1905, Freund treated thebaine with phenylmagnesium bromide and obtained a new base phenyldihydrothebaine (called hereafter p.d.h.t) which was just thebaine to which the elements of benzene (C_6H_5,H) had been added. This reaction has never been satisfactorily explained and on the basis of evidence only recently acquired Robinson (1) has interpreted it as involving the rearrangement of thebaine structure I to structure II which is p.d.h.t.



I



II

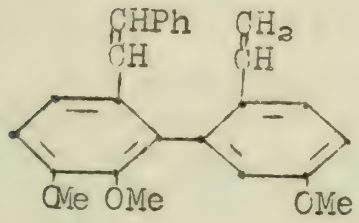
Evidence for Rearrangement.--p.d.h.t. is remarkably stable. It is hard to hydrogenate in the presence of a catalyst (thebaine is easily hydrogenated) and when reduction does occur all that happens is a break of C-N bond. The enol methyl ether in thebaine is easily hydrolyzed but though p.d.h.t. contains this methoxy group, it is not hydrolyzed by hot concentrated HCl. Hot HBr, however, produces the change $(OMe)_2OH \rightarrow (OH)_3$ and on treatment with diazomethane, this trihydroxy compound gives a trimethoxy compound which is the methyl ether of p.d.h.t. This contrast in behavior between thebaine and p.d.h.t. strongly indicates that the near aromatic nucleus of thebaine which carries the hydrolysable methoxyl has become truly aromatic in p.d.h.t.

p.d.h.t. is optically active and Hofmann's exhaustive methylation gives a series of optically active derivatives; this is true even of the second stage in which nitrogen is eliminated. The nitrogen free optically active compound has two double bonds which are detected easily.

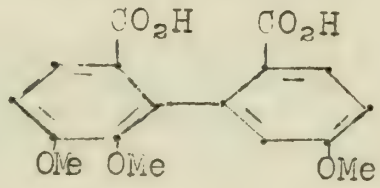
p.d.h.t. is a C_{25} base and one carbon is attached to nitrogen as $N-CH_3$ (which is lost by Hofmann's exhaustive methylation), two carbons are in -OMe groups and by assumption 18 C's are in three benzene rings (2 of the thebaine skeleton and the phenyl group introduced by the reagent); that leaves only 4 C's for the 2 double bonds. Hence exhaustively methylated p.d.h.t. cannot contain an asymmetric carbon atom and its optical activity must be due to asymmetry about the molecule as such. This molecule is most likely a restricted biphenyl molecule because of the ease with which thebaine and its derivatives are degraded to phenanthrene derivatives which in turn are derived from biphenyl.

That p.d.h.t. contains 2 and only 2 sources of dissymmetry has been demonstrated by isolation of two stereoisomers designated (+) α and (+) δ. Heating partially converts one to the other until an equilibrium is reached. Thus, at least one asymmetric center is relatively unstable. Degradative hydrogenation of (+) α and (+) δ p.d.h.t. to (+) phenyltetrahydrothebaimine and the corresponding conversion of (-) δ and (-) α to (-) phenyltetrahydrothebaimine show that (+) α differs from (-) α [so also does (+) δ differ from (-) δ] in having the opposite configuration at the source of dissymmetry other than the carbon attached to nitrogen, i.e. in the biphenyl part of the molecule.

The nine membered ring in formula II allows the phenyl nuclei to be disposed at right angles or at any intermediate angle without strain. The ultraviolet absorption of p.d.h.t. gave no indication whatever of the appearance of a new aromatic ring in conjugation with the first. This is however explicable when it is considered p.d.h.t. is a restricted biphenyl since all such restricted biphenyls have been shown to exhibit abnormal ultraviolet spectra (3,4) not characteristic of biphenyl. Chemical studies have confirmed the structure. Oxidation of p.d.h.t. with $KMnO_4$ gives benzoic acid, benzaldehyde and 4-methoxyphthalic acid. Exhaustive methylation of the methyl ether of p.d.h.t. gives an optically active compound III which on further oxidation gives a trimethoxy diphenic acid (IV).



III



IV

Mechanism of the Rearrangement.--The migrating ethanamine chain is cationoid, (c) is joined to (b) by means of the electrons of the link (a,b); the electrons in (c,d) go to (d,e) to meet the demands of the aromaticity of the nucleus; electrons (e,f) are taken by the oxygen atom which acquires a negative charge; the phenyl anion brings a new electron pair to (a) replacing those lost to the migrating group (c). This series of changes can be assumed to start at either end; i.e. attack by pH: or assumption of a negative charge by oxygen. The driving force behind the rearrangement is most certainly the tendency of the near aromatic group to become fully aromatic. The formation of isomers is due to the arrangement of the -CHPh- group in each of the two possible senses, the diphenyl skeleton being constructed in one sense only.

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Reported by S. Swaminathan
April 9, 1948

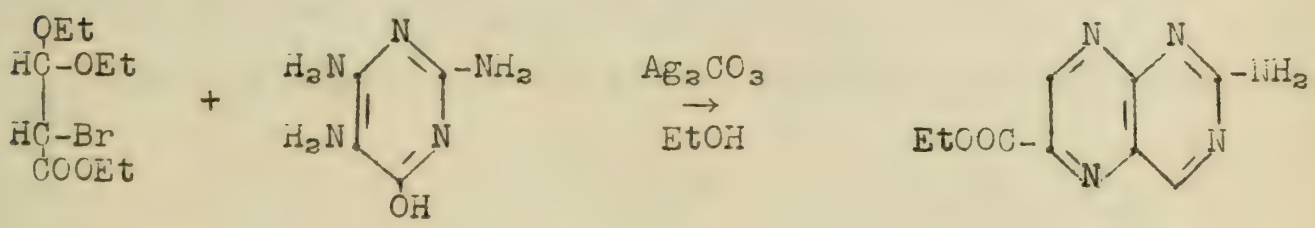
PTEROYLGLUTAMIC ACID (FOLIC ACID)

Within recent years, several crystalline anti-anemia factors have been isolated from liver, yeast, and from a fermentation process. They havebeen variously designated as vitamin B_c (1,2), vitamin B_c conjugate (3), liver L. casei factor (5,6), and fermentation L. casei factor (8,9). The various factors are closely related and the name "folic acid" has been applied indiscriminately to members of the group. It has been shown that liver L. casei factor is identical to vitamin B_c (4). The fermentation L. casei factor and vitamin B_c conjugate are peptide conjugates of this simpler factor and yield two and six additional molecules of l(+)-glutamic acid, respectively, on hydrolysis.

The isolation of the factors was in general accomplished by adsorption on activated charcoals and subsequent elution and purification. Progress of the purifications was followed by microbiological assay; the factors promote the growth of "Lactobacillus Casei".

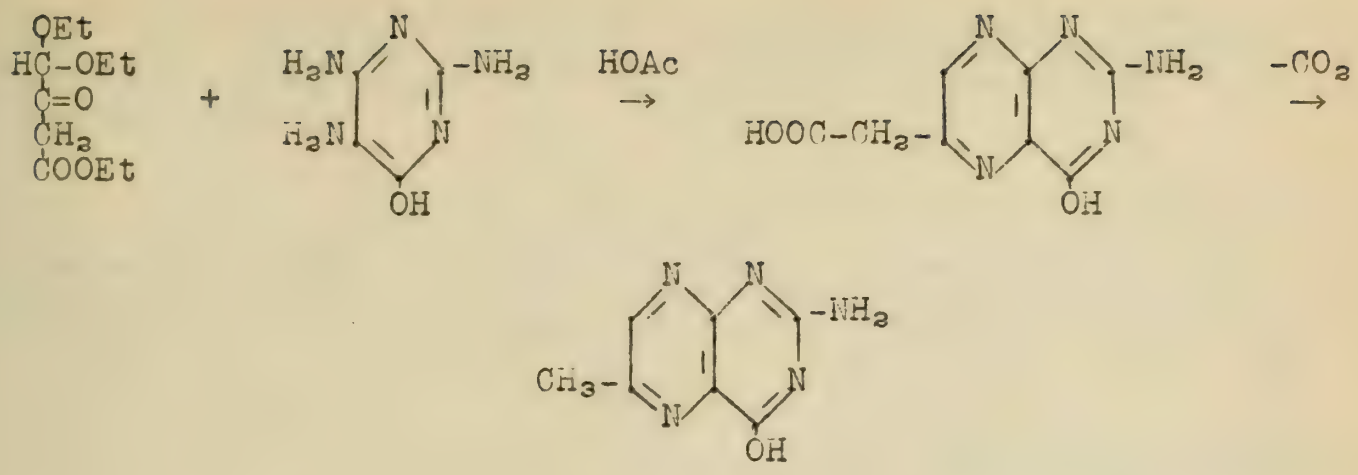
Degradation studies have been made on fermentation L. casei factor. Upon alkaline hydrolysis in the absence of oxygen, liver L. casei factor and two moles of a dicarboxylic α-amino acid resulted (7). The liver L. casei factor was shown to be present by its biological activity and ultra-violet absorption spectra.

Upon alkaline hydrolysis of the fermentation L. casei factor in the presence of oxygen, biological inactivation occurred. A fluorescent pigment and a diazotizable aromatic amine was isolated. The pigment was proved by synthesis to be 2-amino-4-hydroxypteridine-6-carboxylic acid (11).



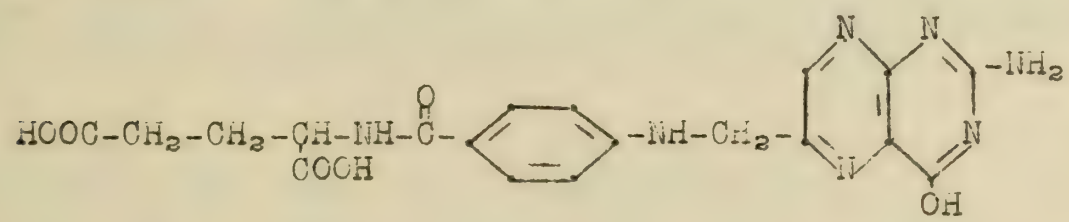
The aromatic amine gave p-aminobenzoic acid and an α-amino acid upon further hydrolysis.

Hydrolysis of the fermentation L. casei factor by sulfurous acid gave a pteridine fraction and another diazotizable aromatic amine (10). The pteridine fraction was not isolated but reacted readily with aldehyde reagents, and on standing in dilute alkali disproportionated to yield 2-amino-4-hydroxypteridine-6-carboxylic acid and 2-amino-4-hydroxy-6-methylpteridine. The latter was also synthesized (11).



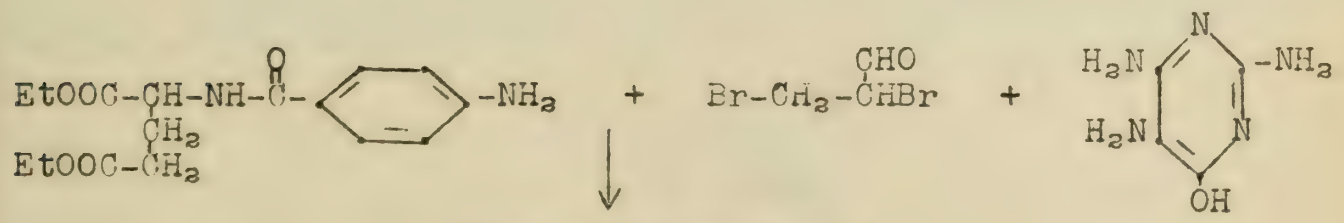
On oxidation, the 6-methyl compound gave the corresponding carboxylic acid, the other disproportionation product. The aromatic amine was further hydrolized to p-amino benzoic acid and three moles of glutamic acid.

On the basis of the degradation products, the following structure was assumed to liver L. casei factor.



The compound has been given the name "Pteroylglutamic Acid" and has been synthesized by several methods.

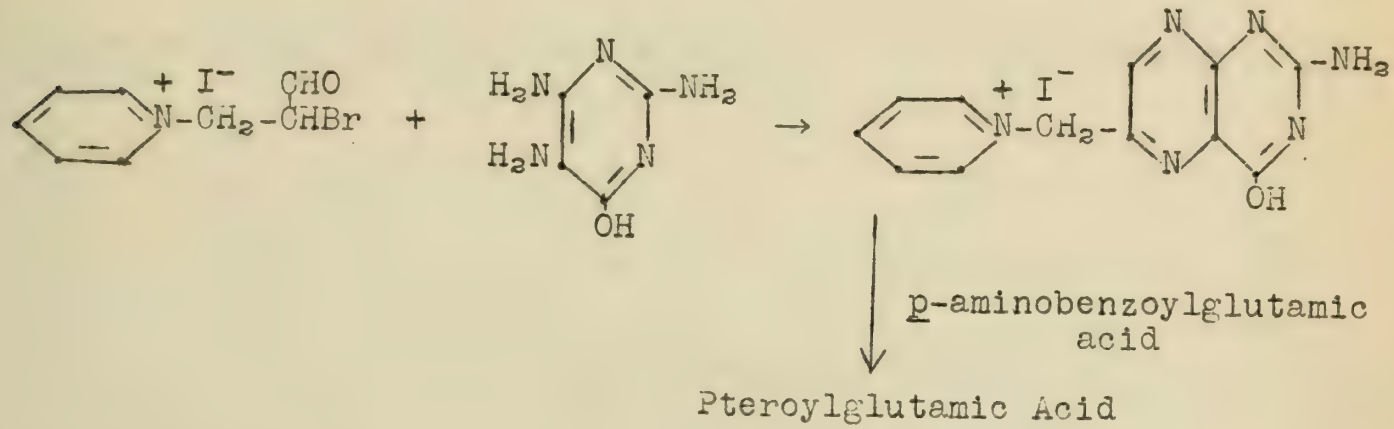
The first synthesis was accomplished in the following manner (12).



Pteroylglutamic Acid

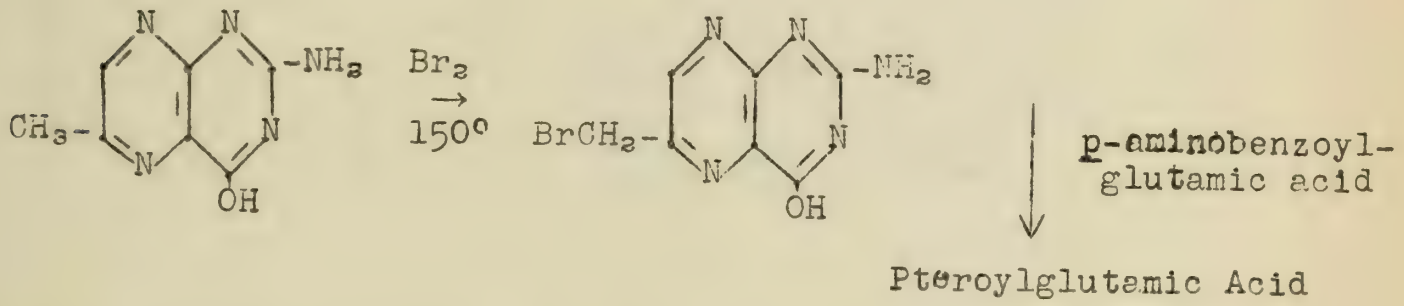
A 30-50% yield of crude product was obtained which was shown by bio-assay to contain 10-25% pteroylglutamic acid. The product was purified and shown to be identical in every respect with the factor isolated from liver.

Synthesis of pteroylglutamic acid by way of a 6-substituted pteridine afforded a stricter structure proof of the compound (13). p-Aminobenzoylglutamic acid was alkylated by means of a quaternary pyridinium salt.

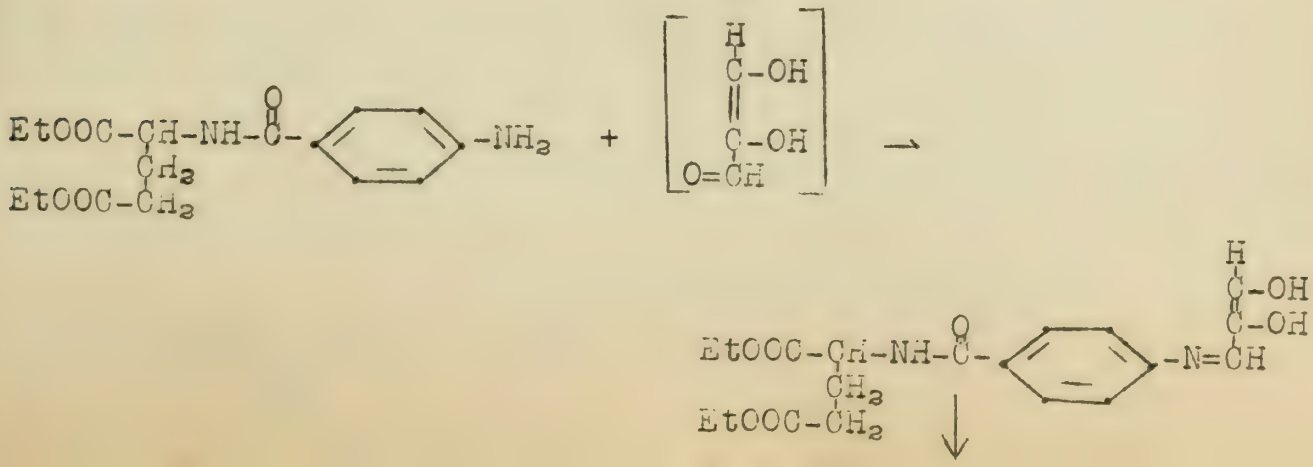


Pteroic acid was synthesized by similar alkylation of p-aminobenzoic acid.

It was found that 2-amino-4-hydroxy-6-methylpteridine could be monobrominated on the methyl group and the resulting bromo compound used to alkylate p-aminobenzoylglutamic acid (15).



A convenient synthesis of the 6-methyl compound was the reduction of the quaternary pyridinium iodide used in the previous synthesis. Another method of synthesis makes use of "reductone", 2,3-dihydroxyacrylaldehyde (14).



↓ 2,4,5-triamino-6-hydroxypyrimidine

Pteroylglutamic acid

An overall 12% yield of pteroylglutamic acid was obtained by this method.

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Reported by John B. Campbell
April 16, 1948

THE PARACHOR IN ORGANIC CHEMISTRY

Theory.--The term "parachor" implies comparative volumes. It is one of the best measures of molecular volume that has yet been devised.

In 1923 Macleod derived the empirical equation

$$\frac{\gamma^{1/4}}{D-d} = C$$

(γ = surface tension, D = density of liquid, d = density of vapor, C is a constant for a given substance) and showed that it held nearly exactly for a large number of substances. Ferguson, in the same year, was able to derive the same relationship from theoretical considerations. In 1924, Sugden, by multiplying both sides of the equation by M, the molecular weight, obtained

$$\frac{M\gamma^{1/4}}{D-d} = MC = [P]$$

and called the resulting constant, [P], the parachor.

The density of the vapor is generally negliable and the equation thus reduces to

$$[P] = \frac{M\gamma^{1/4}}{D} \qquad \text{or} \qquad [P] = V\gamma\ 1/4$$

where V is the molecular volume. A comparison of the parachors of two substances is thus equivalent to the comparison of molar volumes under the best theoretical conditions - those conditions in which they have the same surface tension.

In 1929 Hammick and Andrews found that in solutions the parachor of the solute and solvent are additive and that thus the parachor of the solute in a solution can be found.

Historical.--Sugden investigated hundreds of compounds and showed that the parachor was primarily an additive quantity. By adding together the parachors he obtained for various atoms and for various structural groups such as the double bond, the triple bond, the three membered ring, etc., he was able to obtain calculated values for parachors of compounds that agreed very closely with those found by experiment. The parachor was then applied to structure proofs in those cases in which the different suggested

structures had different molecular volumes and were thus distinguishable. These investigations had considerable success in helping to prove the structure of benzene, paraldehyde, quinone, the dimer form of acetic acid, the chelation in salicylaldehyde and structures in numerous other compounds. In some cases where more than one type of bond is possible, results obtained from parachors have been shown to be erroneous. The parachor predicts a cyclic structure in azides whereas x-rays and electron diffraction patterns show a linear structure to be present.

Present Work.--The parachor was used extensively for some time, but gradually its value began to be doubted as evidence accumulated that in many cases the differences between calculated and experimental values exceeded experimental errors. It was recognized that the parachor was not strictly an additive quantity but also a constitutive one. Gibling, in England, and Quayle, in this country, have evaluated these constitutive differences and now claim that the parachor is a more powerful tool than before. They found that in proceeding along a homologous series the differences between the calculated and experimental values for the parachors varied in a regular manner. Gibling has expressed his results in the form of mathematical formulae and Quayle in the form of tables. From these the parachors of many types of compounds can be calculated to an accuracy of 0.2%.

The constitutive factors that influence the parachor are the branching of the chain, polarity in the molecule, substituent groups, and the length of the chains. Branching brings carbon atoms in closer to one another and brings about a decrease in molecular volume as opposed to a straight chain. A polar group, such as a carbonyl group, will make its effect felt as far as four carbons along the chain and thus bring about a change in volume. Lengthening of the chain brings about an increase in the parachor above that calculated.

The simplest parachor to calculate is that of a straight chain saturated hydrocarbon. Gibling gives the equation:

$$[P] = [2c+(n-2)k]f^n$$

(c is the parachor for the terminal CH_3 groups, k is the value for the CH_2 group, n is the number of carbons, f = 1.0004165). To calculate the parachor for any other type of hydrocarbon, values for branching and unsaturation must be inserted. Parachors for compounds of other series can be calculated by inserting values for the functional groups. The quantity f^n takes care of the increase in volume due to lengthening of the carbon chain. The quantity in brackets is called the "standard value" and is similar to the parachor as calculated by Sugden. The difference between the parachor and the standard value is called the "expansion coefficient". For the straight chain hydrocarbon in which n = 20, the E.C. = 6.92.

For a compound other than a straight chain hydrocarbon, the S.V. is first calculated, then the E.C. is taken from a table of corrections for the n-paraffins, and added to the S.V. to obtain the parachor.

Example:

β-isoamylene $CH_3-CH=C(CH_3)_2$

$3CH_3$(c) at 55.2	=	165.6
(c)-CH=(c) at 34.3	=	34.3
(c)=C(C)(C) at 16.7	=	16.7
Standard Value	=	216.6
E.C. from table	=	+ 0.4
[P]	=	217.0

For a carbonyl compound, a standard value is calculated as above, using a parachor for the carbonyl group obtained from a table and negative correction factors to compensate for the effect of the carbonyl group on the attached alkyl groups. Parachors for other types of compounds are calculated in an entirely analogous manner.

Uses.--The parachor can be used in structure proofs as in the examples already cited. It can be used to show how much branching of the carbon chain exists. It has been used for distinguishing between cis-trans isomers in the cyclohexane series.

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Reported by Robert E. Berry
April 16, 1948

THE STEREOCHEMISTRY OF ARSONIUM AND PHOSPHONIUM COMPOUNDS

The resolution into optically active forms of phenylmethylbenzylallylammonium iodide by Pope and Peachy (1) and the subsequent resolution of several other quaternary ammonium salts of this type leave little doubt that similar arsonium and phosphonium salts should also be susceptible to optical resolution.

Nevertheless, no phosphorous compound of the type $(abcdP)^+X^-$, where a,b,c, and d represent alkyl or aryl groups and X^- a univalent acid radical has been resolved. Although several attempts (2,3,4) have been made to resolve similar arsenic compounds, only two were successful and in both cases, the arsenic salt possessed only a very small and fleeting rotation. Burrows and Turner (5) resolved phenyl-α-napthylbenzylmethylarsonium iodide which possessed a fleeting rotation, the highest value being $[M]_D$ +12. Kamai (6,7) prepared p-tolylbenzylethyl-n-propylarsonium iodide having $[M]_D$ +45, which rapidly racemized in solution.

Burrows and Turner (5) obtained strong evidence that quaternary arsonium iodides, analogous to quaternary nitrogen compounds, give rise to the following dissociation equilibrium:

$$(abcdAs)^+I^- \rightleftarrows abcAs + dI$$

They attributed the difficulty of obtaining optically stable halides to the ready formation of this equilibrium. A similar argument could be put forward to explain the lack of success attending some of the many attempts to resolve quaternary phosphonium salts (8,9,10), but in the majority of the cases investigators have been hampered by the difficulties involved in the crystallization of phosphonium salts with optically active anions (8,9,11,12,13,14).

The above dissociation theory of optical instability could be tested by the attempted resolution of a salt $(abcdAs)^+X^-$, in which a,b,c, and d were different aryl groups, or of an arsonium compound which for structural reasons could not dissociate in solution. The required dissymetric tetra-arylarsonium salt has been prepared by Mann and Watson in the following manner:

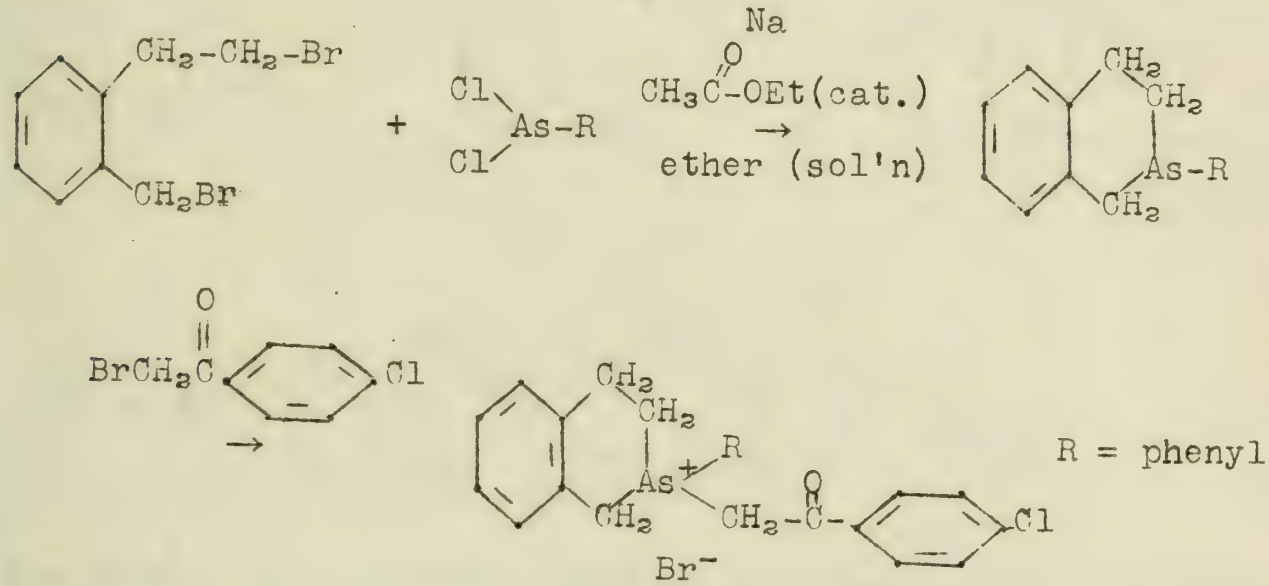
$$PhAs{:}O \xrightarrow{p\text{-}MeC_6H_4N_2OH} Ph(p\text{-}MeC_6H_4)AsO(OH) \xrightarrow{SO_2+HCl} Ph(p\text{-}MeC_6H_4)AsCl$$

$$\xrightarrow{p\text{-}ClC_6H_4MgI} Ph(p\text{-}MeC_6H_4)(p\text{-}ClC_6H_4)As \xrightarrow[AlCl_3]{m\text{-}MeC_6H_4Br}$$

$$[Ph(p\text{-}MeC_6H_4)(m\text{-}MeC_6H_4)(p\text{-}ClC_6H_4)As]^+Br^-$$

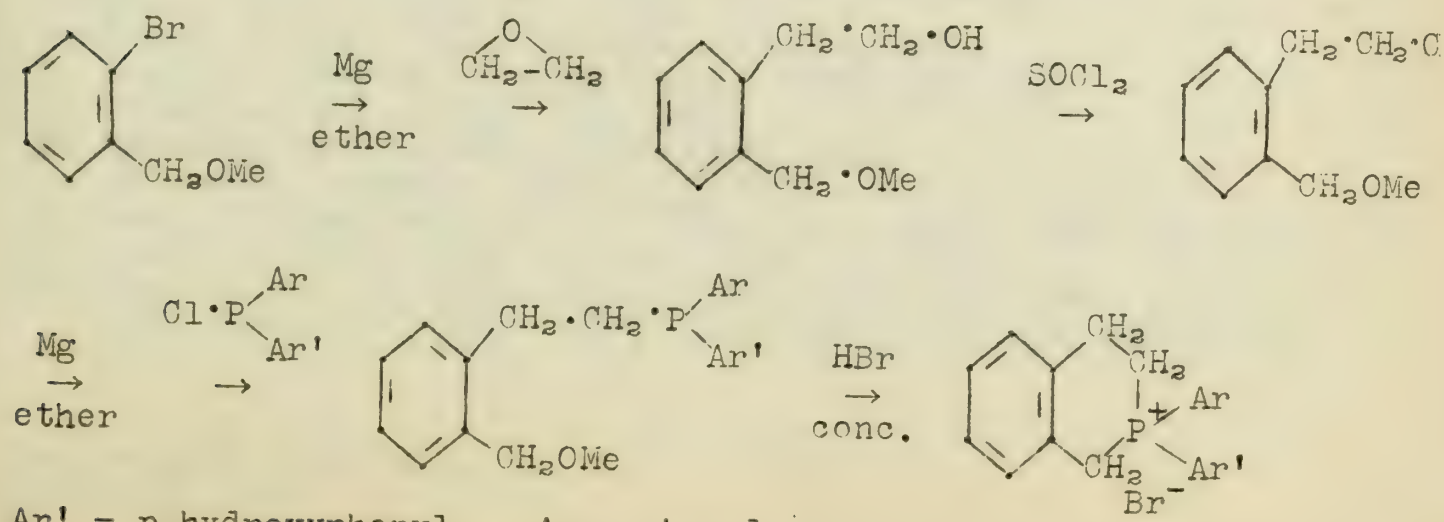
The salt was converted into the crystalline and less soluble iodide, but no report has been made that it has been resolved.

2-Phenyl-1,2,3,4-tetrahydroisoarsinoline (15) was treated with p-chlorophenacyl bromide to yield the highly crystalline 2-phenyl-2-p-chlorophenacyl-1,2,3,4-tetrahydroisoarsinolinium bromide, a salt containing an asymetric arsenic atom which is stable in solution (16).



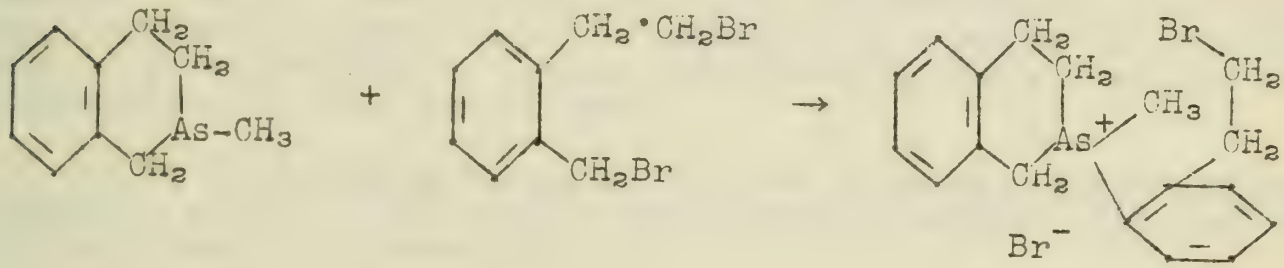
The salt was resolved through the bromocamphorsulfonate and an optically pure picrate $[M]_D$ -450° (in chloroform) and an iodide $[M]_D$ -354° were obtained. The 1-isoarsinolinium iodide underwent no perceptible racemization in chloroform solution at 15° during five days if protected from bright light, which caused slight photochemical decomposition.

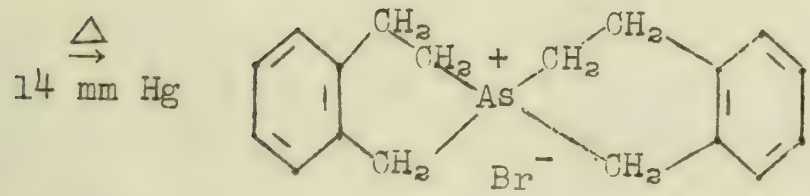
The difficulty in synthesizing the phosphorous analog of the above arsonium compound caused Mann (17) to attempt the resolution of a slightly different type of phospholinium compound, synthesized in the following manner:



The d-isophospholinium bromide, having $[M]_D$ +32.9 was isolated on one occasion, but could not be repeated. These subsequent failures were attributed to the formation of partial racemates.

As-spiro-bis-1,2,3,4-tetrahydroisoarsinolinium bromide (18) was prepared:





The arsenic atom in this compound is symmetric, but the disposition of the ring systems around this tetrahedral atom cause the compound to possess molecular dissymetry. It was resolved and the d- and l-iodides isolated having $[M]_D$ +342° and -344° in chloroform solution. The stability of the hetereocyclic system gives the compound high optical stability.

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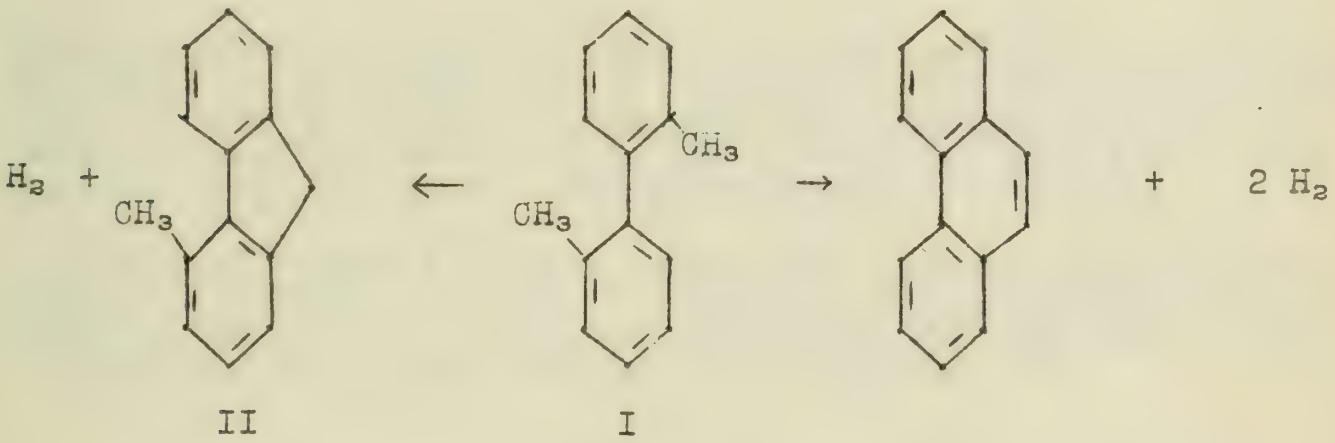
Reported by Emmett Burk
April 16, 1948

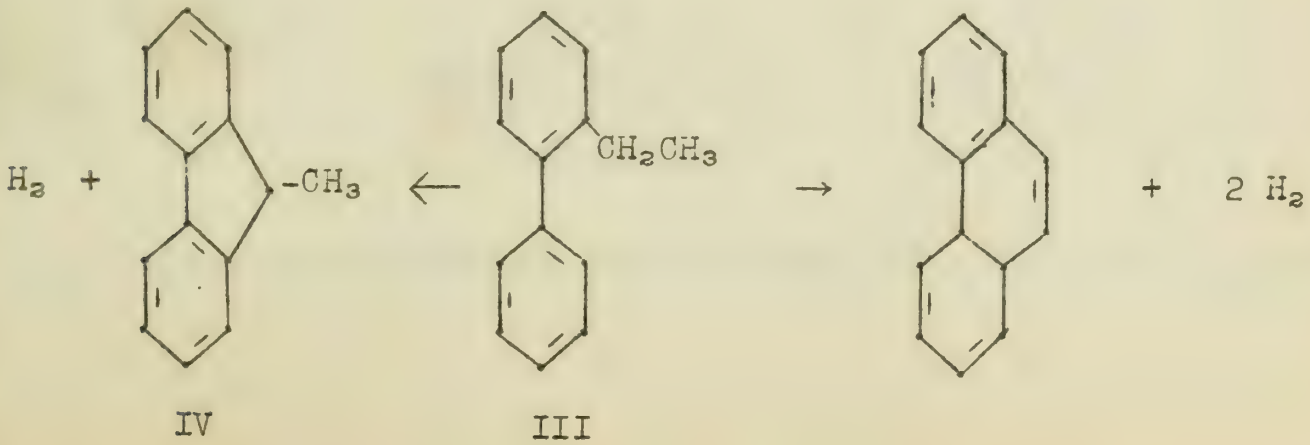
CYCLODEHYDROGENATION

Cyclodehydrogenation may be defined as the intramolecular loss of hydrogen from an aromatic or hydroaromatic compound to form a new compound with a greater number of rings. The products obtained by the hydrogenation or carbonization of coal are, in part, assumed to be present in the original coal structure and to arise from the catalytic or thermal "depolymerization" of coal. Orchin, of the Bureau of Mines, became interested in the possibility that some of the condensed aromatic nuclei obtained from coal by these processes result from less highly cyclic structures by thermal or catalytic intramolecular loss of hydrogen.

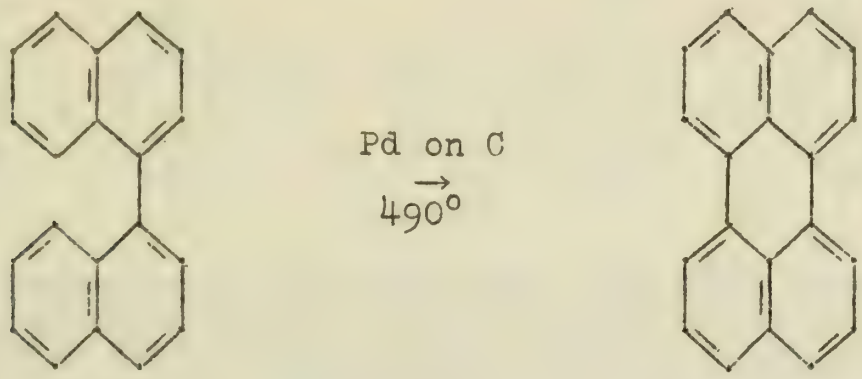
When 2,2'-dimethylbiphenyl (I) was treated with palladium on charcoal at 450°, the product was 4-methylfluorene (II), and no phenanthrene was formed (1).



The fact that no phenanthrene was isolated is of interest. Apparently, the product depends upon whether the operation is in liquid or vapor phase and whether the reaction is a pyrolysis, a catalytic reaction or a chemical reaction. Berger was able to obtain a 50 per cent yield of phenanthrene by heating I with S. A similar treatment of 2-methylbiphenyl with palladium gave fluorene, with a yield of 35 per cent (2).

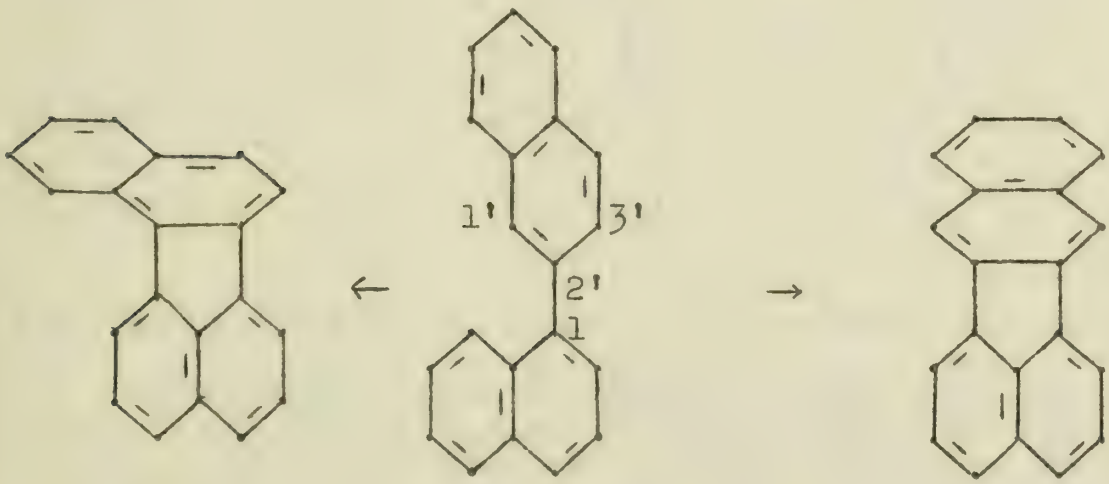


A new synthesis of perylene has been developed by Orchin. 1,1'-Dinaphthyl, when passed over Pd at 490°, gave a 10 per cent conversion to perylene (4).



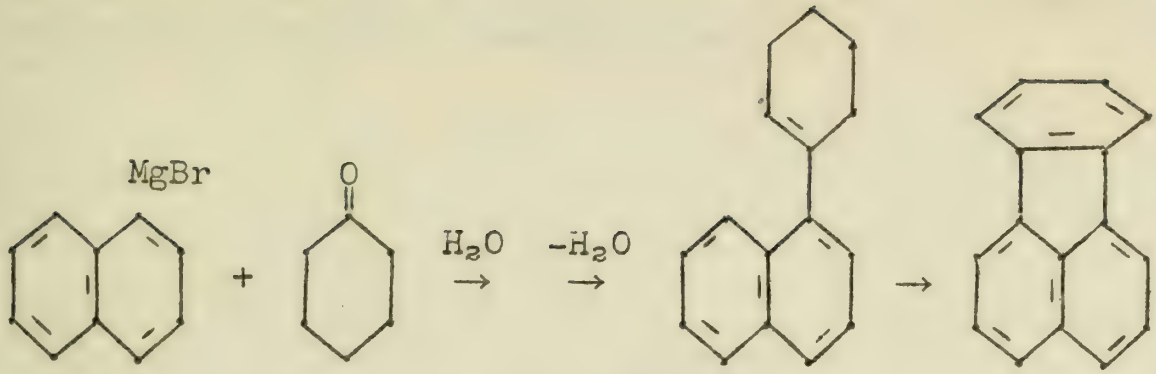
This procedure has an advantage over other methods of closing down the rings of dinaphthyl due to the fact that unconverted starting material can be recovered unchanged and used again. Scholl and Seer employed $AlCl_3$ at 140° to obtain a 15 per cent conversion, but the remainder of the starting material was lost (5).

1,2'-Dinaphthyl (V) was passed over chromia-alumina at 500°, and cyclizations at 1' and 3' occurred. Two compounds were isolated, but more of the 7,8-benzfluoranthene (VI) was found. Ring closure was at the more reactive 1' position.



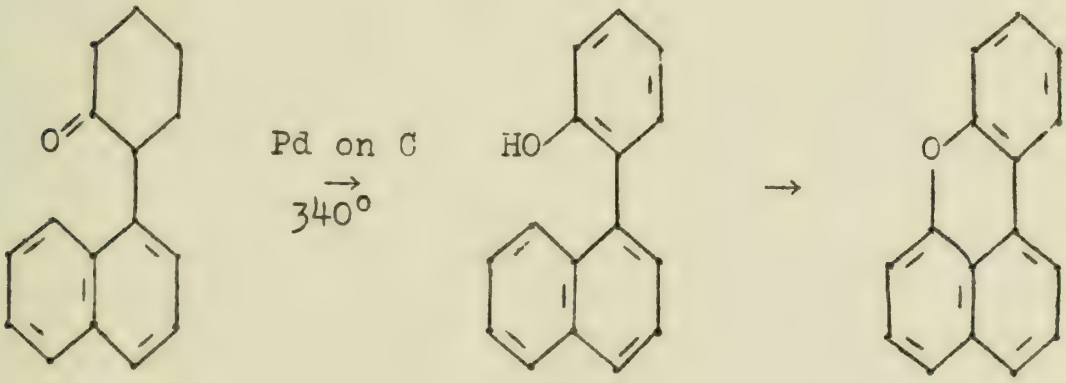
VI V

Pure fluoranthrene is now available in a three step synthesis (6)



The cyclodehydrogenation shown above was best done over pellets of alumina-chromia at 520°. The yield was 31 per cent per pass, with a recovery of 40 per cent of the starting material. The ease with which the tetrahydro compound can be converted to fluoranthrene contradicts the rule that dehydrogenation of this type of molecule results in aromatization without ring closure. The conditions used here were more drastic than those commonly used in the past.

The most recent work by Orchin in this field was the synthesis of ring oxygen compounds. The following procedure was employed for preparing 1,9-benzoxanthene (8).



The yield, based on the keto compound, was 6 per cent.

o-Phenylphenol gave diphenylene oxide in 8 per cent yield. Biphenyl was also isolated, indicating that the hydrogen liberated in ring closure was utilized in hydrogenolysis. When the reaction was carried out in a sealed tube, the yield was 14 per cent for the oxide, with 8 per cent biphenyl, and the remainder was unconverted phenylphenol.

The Orchin method of cyclodehydrogenation is a useful synthesis of polynuclear aromatic compounds. It supplements the Scholl reaction, and in many cases is an improvement. Fluroanthrene had not been prepared previously, except in very small yield (7). 1,9-Benzoxanthene has now been synthesized, having previously been isolated in minute amount from coal tar. The

intramolecular loss of hydrogen to form ring oxygen compounds has interesting synthetic possibilities.

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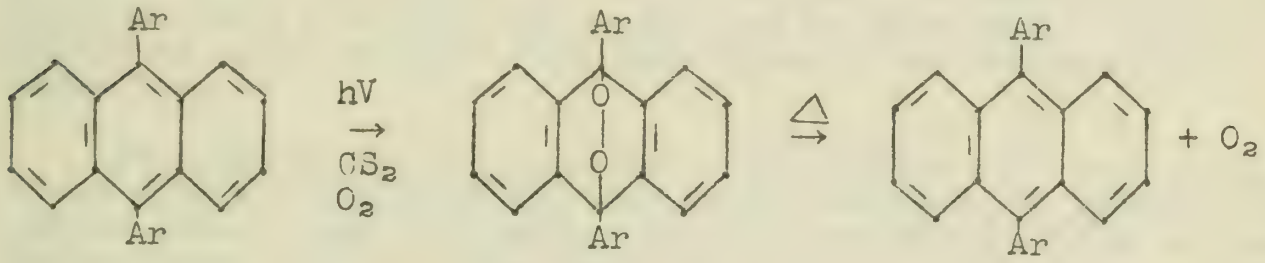
Reported by C. B. Thompson
April 16, 1948

SOME AROMATIC TRANSANNULAR PHOTOOXIDES

Introduction.--Certain polynuclear aromatic compounds in the presence of light and oxygen are observed to spontaneously undergo peroxide formation. The product of such a reaction is called a photooxide. Aromatic photooxide formation is largely restricted to systems containing an anthracene nucleus, though this is not always true. The formation of such a photooxide does not occur however when either a phenanthrene or naphthalene structure is irradiated in the presence of oxygen (1). It has thus been assumed that photooxidation is a different phenomenon from the photoaccelerated autooxidations observed in numerous unsaturated compounds.

Photooxyanthracenes.--In the anthracene system the peroxide group has been indicated as assuming a transannular position between the 9 and 10 positions, a structure which is supported by spectroscopic studies (2). The photooxyanthracenes which have been prepared, with the exception of those not substituted in the 9 and 10 positions by aryl groups, will generally undergo dissociation into oxygen and the compound from which the photooxide was prepared. Such a dissociation often results in the release of most of the oxygen bound in the transannular position, and can be accomplished by heating the photooxide.



1.

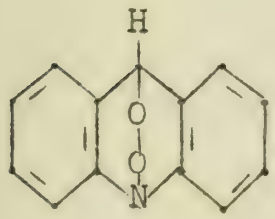
Anthracene itself is rather sensitive to light. If it is irradiated for one hour in a carbon disulfide solution, a white crystalline photooxide is produced in a 70% yield. This photooxide if exposed to further irradiation is unstable, and degenerates into a resin. Photooxyanthracene decomposes explosively at 120°C, yielding no oxygen (3).

The position and type of substituents on the anthracene nucleus are closely associated with the stability of the photooxide produced, as indicated by the temperature at which the photooxide dissociates. The most stable photooxides have been prepared from anthracenes containing aromatic substituents in the 9 and 10 positions, and a rather large number of 9,10-diphenylanthracenes have been photooxidized. 9,10-Diphenylanthracene itself photooxidizes in a 90% yield, producing a photooxide which will give up 95% of its oxygen when heated to 180°C (4). In general, substituents in the 1 and 4 positions in the 9,10-diphenylanthracene complicate the photooxidation process, and lower the yields of photooxide obtainable from the reaction (5). Substituents in the 2 and 3 positions seem to exert a similar, though less marked, influence on the reaction.

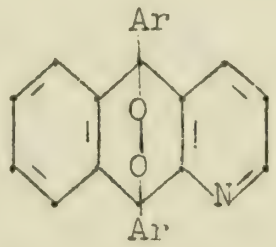
Methoxy groups, if substituted in the same benzene ring in 9, 10-diphenylanthracene, not only tend to lower to yield of the photooxide obtainable, but also cause the photooxide produced to possess less stability. For example, the photooxides of the 2-methoxy, 1-methoxy, 2,3-dimethoxy, and 1,4-dimethoxy derivatives dissociate at 160°, 150°, 120-150°, and 20-25°C respectively (6). On the other hand, chlorine substituted in the same benzene ring in 9,10-diphenylanthracene seems either to have no effect or to increase somewhat the stability of the corresponding photooxide. The 1-chloro, 1-methyl-4-chloro, and 1,4-dichloro derivatives of 9,10-diphenylanthracene dissociate at 180°, 190°, and 200° respectively (5). Enhanced stability is also found in 1,4,9,10-tetraphenylphotooxyanthracene, which dissociates at 200-210° (5).

It has been noted that decreasing the aromatic character of the substituents in the 9 and 10 positions of the anthracene system also complicates the photooxidation reaction. 9,10-Di(2-thienyl) anthracene, when irradiated, forms a very unstable product which is probably a photooxide but which resinifies too quickly to be obtained in the pure state. 9-Phenyl-10-(2-thienyl)anthracene, irradiated gently in a dilute carbon disulfide solution, yields a colorless, easily dissociable photooxide (7). From a comparison of a number of meso alkylphenylphotooxyanthracenes, however, which on dissociation, yield very little oxygen, it has been concluded that the high stability of oxygen can be maintained only in compounds in which the two meso substituents are aromatic in character.

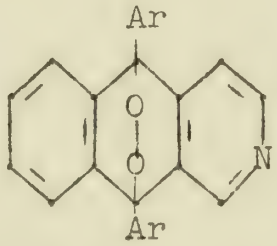
Photooxyazanthracenes.--The substitution of a nitrilo group for a methinyl group in the anthracene nucleus, in general, has no marked effect upon the photochemical properties of the system. Photooxides have been prepared for three general types of azanthracenes, namely the acridines (I), 1-azanthracenes (II), and 2-azanthracenes (III).



I



II



III

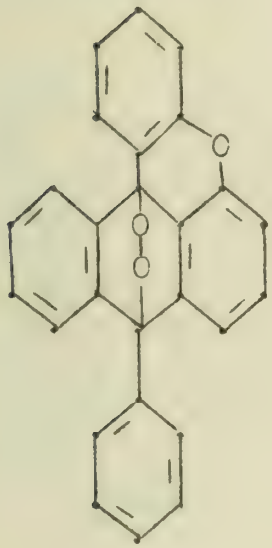
Photochemical studies in the acridine series have been confined largely to 9-phenylacridine and acridine itself. Acridine in a carbon disulfide solution has been observed to slowly adsorb oxygen in the presence of sunlight. If benzene or ether is used as the solvent, a crystalline photooxide can be isolated (8).

9,10-Diphenyl-1-azanthracene unlike 1-azanthracene is readily

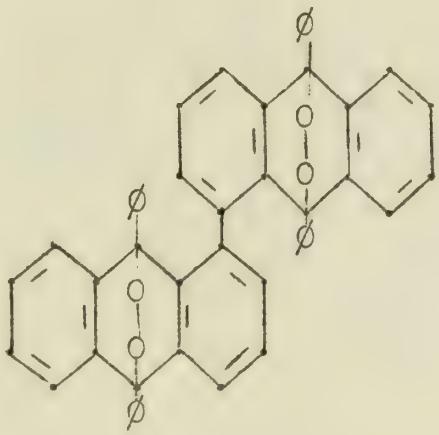
converted into a stable photooxide, for which a structure similar to that assigned to 9,10-diphenylphotooxyanthracene has been assumed (9).

The 2-azanthracenes possess photochemical properties similar to the 1-azanthracenes. Unsubstituted 2-azanthracene yields an isolatable photooxide, whereas 9,10-diphenyl-2-azanthracene is partially converted into a rather unstable photooxide (10).

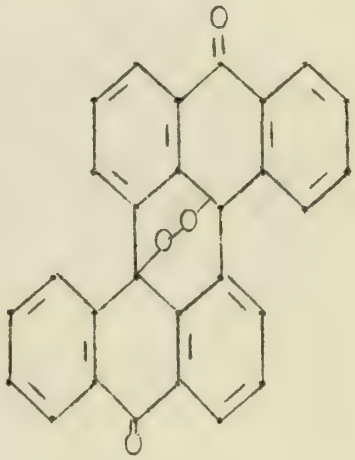
Some Polynuclear Aromatic Photooxides.--Many polynuclear systems which contain an anthracene nucleus readily form stable photooxides.



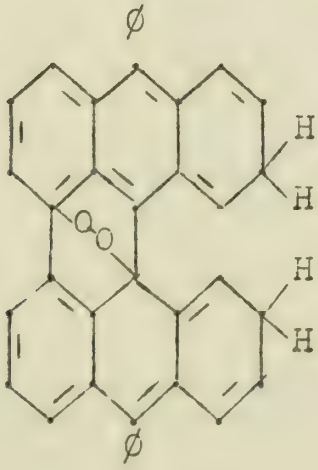
IV



V



VI



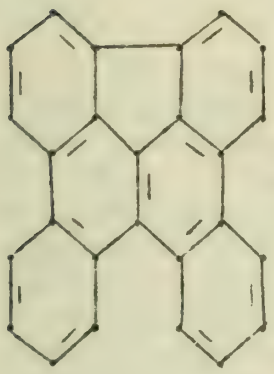
VII

The photooxide (IV) is very sensitive to light. The dissociation of the photooxide occurs at 140° (11).

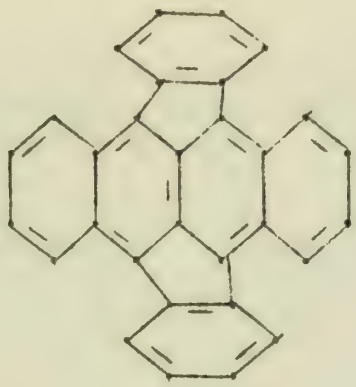
Oxidation in the presence of light of 9,9', 10,10'-tetraphenyl-1,1'-bianthryl occurs readily to yield a diphotooxide (V), which releases 95% of its oxygen at 190°C. This is the only example observed of a photooxide containing two moles of dissociable oxygen (11).

A very rapid photooxidation has been observed to occur with heterocerodianthrone. The photooxide (VI) loses 95% of its oxygen when heated to 150°C (11).

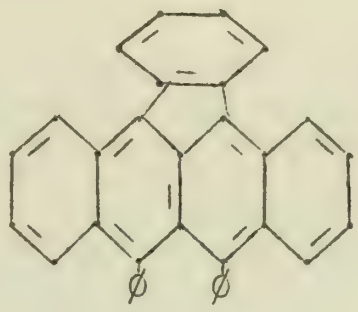
Irradiation of mesodiphenylhelianthrene gives quickly a yellow photooxide (VII), which contains one mole of oxygen. The oxygen in this compound is liberated at 180°C, though the compound does not melt at this temperature. This is the only colored photooxide reported (11).



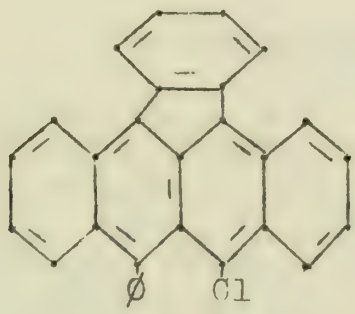
VIII



IX



X

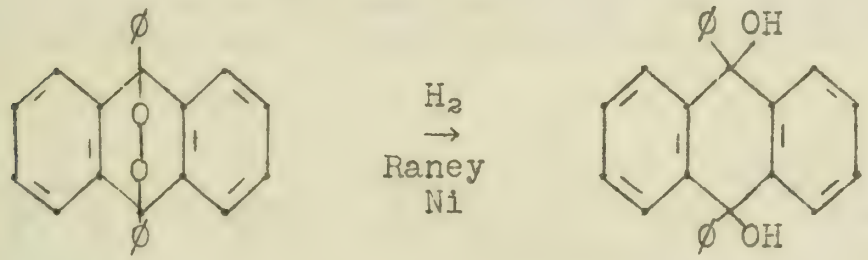


XI

Both rubicene (VIII) and meso diphenylenenaphthacene (IX) are observed not to undergo photooxidation. In contrast, diphenylphenylene naphthacene (X) and chlorophenylphenylenenaphthacene (XI) photooxidize readily. The photooxides of these two latter compounds decompose violently at 150°C and 90°C respectively. The formation of labile oxygen-carbon bonds is promoted by the extension of a polynuclear system by means of a six-membered ring, whereas the opposite effect is obtained with a five-membered ring.

Chemical Properties.--Though aromatic photooxides decompose when heated, the transannular peroxide arrangement often exhibits considerable stability. In 3-acetyl-9,10-diphenylphotooxyanthracene, the peroxide bond is so stable that the phenylhydrazone derivative of the photooxide can be prepared directly (13).

Reduction of a photooxide usually leads to the meso dihydroxy derivative.



2.

Photooxidation must often compete with the process of photodimerization, especially with anthracenes not substituted in the meso positions by aryl groups. For example, anthracene, irradiated in ether rather than in carbon disulfide, is largely converted into a photodimer, with only a small amount of the photooxide being produced by the reaction. Dufraisse has postulated that photooxidation and photodimerization are initially not antagonistic, however, but proceed by means of a common intermediate. For tetraphenylnaphthacene, it has been suggested that the photooxidizable intermediate is not the simple naphthacene or its diyl form, but an unstable dimer, from which the photooxide splits out, under the proper conditions, with the elimination of the free naphthacene.

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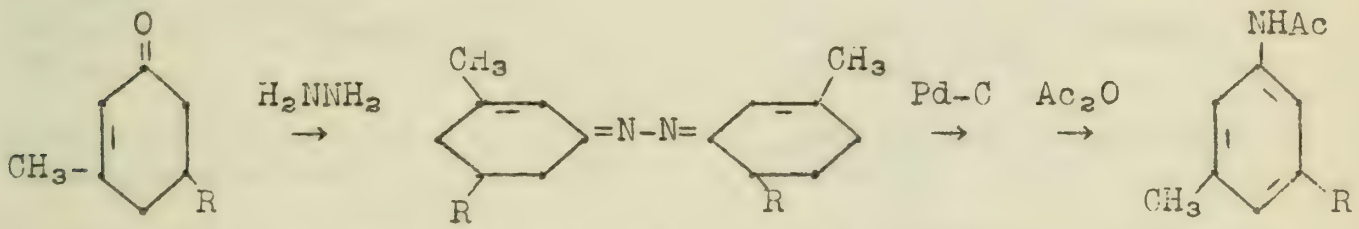
Reported by J. N. Coker
April ~~16~~, 1948
23

CATALYTIC DEHYDROISOMERIZATION

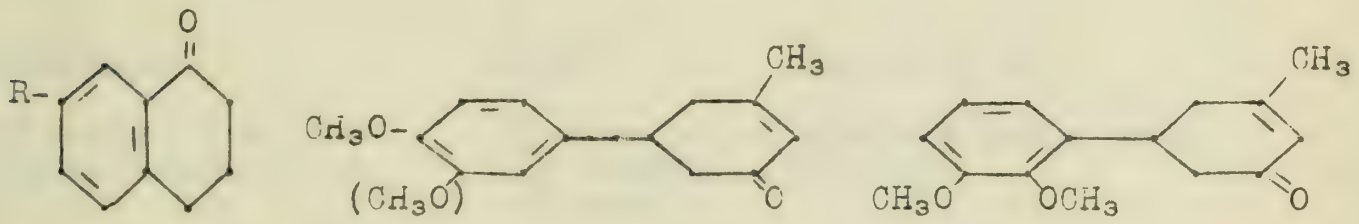
The course of dehydrogenation reactions involving alicyclic compounds is often considerably influenced by the presence of functional groups. Hydrogenation catalysts have the ability to transfer hydrogen from one portion of a molecule to another without the aid of molecular hydrogen. This process offers a convenient route to aromatic compounds which are difficult to obtain by the ordinary methods of aromatic substitution.

Azines derived from substituted cyclohexenones can be converted into aromatic amines by the use of 5% palladium on charcoal as a catalyst and triethylbenzene as a solvent (1).



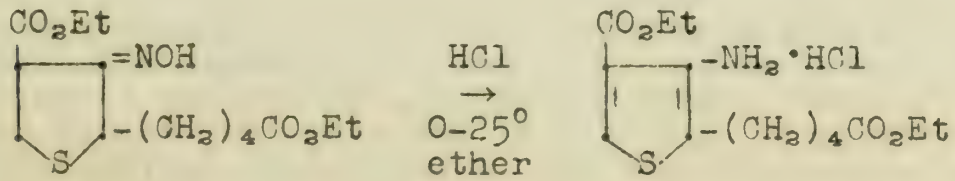
R = CH_3; C_2H_5; i-C_3H_7; n-C_3H_7; i-C_4H_9 (50%)

Aminobiphenyls and naphthylamines can also be obtained from the corresponding azines by the same process in yields of 55% and 20%, respectively (2). The yields are based on the pure acetyl derivatives. The parent ketones are illustrated below:



R = CH_3; C_2H_5; H

The reaction appears to be general for the preparation of aromatic amines, and the alicyclic ketones are obtained by conventional methods (3,4). Attempts to dehydrogenate the oximes and semicarbazides of these ketones to the amines failed; however, alicyclic oximes can be converted into aromatic amines in good yield by the use of hydrogen chloride in various solvents (5).

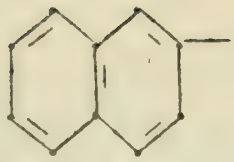


(61%)

Alicyclic ketones are transformed into the corresponding phenols under the influence of dehydrogenation catalysts. The first example of this reaction was reported by Darzens and Levy in 1932, whereby α-tetralone was converted into α-naphthol by the use of sulfur or selenium (6). The recent work on this problem is summarized in the following table:

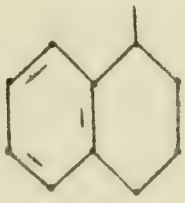
Compound	Catalyst	Product	Ref.
7-methyltetralone-1	Pd-C(310°)	7-methyl-1-naphthol (60%)	7
4'-keto-1',2',3',4'-tetrahydro-1,2-benzpyrene	S	4'-hydroxy-1,2-benzpyrene (19%)	8
3-methyl-5-alkyl-2-cyclohexene-1-one	S	3-methyl-5-alkylphenol (26-29%)	9
2,3-diphenyltetralone-1	S (300°)	2,3-diphenyl-1-naphthol (95%)	10
1-keto-1,2,3,4-tetrahydrophenanthrene	Pd (in boiling naphthalene)	1-phenanthrol (86%)	11
2,6-diethylcyclohexanone	$Ni-Cr_2O_3$ (350°)	2,6-diethylphenol (50%)	12
menthone	$Ni-Cr_2O_3$ (350°)	thymol (63%)	12
3-methyl-5-aryl-2-cyclohexene-1-one	Pd-C(in boiling triethylbenzene)	3-methyl-5-arylphenol (70-85%)	13
2,6-dibenzalcyclohexanone	Pd-C (240°)	2,6-dibenzylphenol (91%)	14
carvone	Pd-C (232°)	carvacrol (92%)	14

The dehydrogenative isomerization of alicyclic compounds containing exocyclic functional groups has been the subject of recent investigations by Newman and coworkers (15,16). These authors were able to make three generalizations with regard to the treatment of 2-substituted-5,6,7,8-tetrahydronaphthalenes with 20% palladium on charcoal; namely, (a) that a carbomethoxy group is not affected by the hydrogen removed from the ring, (b) a carbonyl group next to the ring is reduced to a methylene group, and (c) a carbon to oxygen single bond adjacent to the ring is hydrogenolized. These generalizations were based on the following experimental evidence (15):

Ar =  Ar' = 

$Ar(CH_2)_nCO_2CH_3$ n=0,1,2,3	$\xrightarrow{Pd-C}$	$Ar'(CH_2)_nCO_2CH_3$	(90%)
$ArCOCH_3$	$\rightarrow$	$Ar'CH_2CH_3$	(63%)
$ArCOCH_2CH_2CO_2CH_3$	$\rightarrow$	$Ar'(CH_2)_3CO_2CH_3$	(70%)
$Ar\overline{CHCH_2CH_2COO}$	$\rightarrow$	$Ar'(CH_2)_3CO_2H$	(71%)
$ArCH_2OH$	$\rightarrow$	$Ar'CH_3$	(67%)

The behavior of 1-substituted-1,2,3,4-tetrahydronaphthalenes in the presence of palladium on charcoal is different in some respects from that of the 2-substituted-5,6,7,8-tetrahydronaphthalene derivatives. A few examples are indicated below (16):

R =  R' = 

RCH_2CH_2OAc	$\xrightarrow{Pd-C}$	$R'CH_2CH_2OH$ $R'CH_2CH_3$	(62%) (28%)
$RCH_2CO_2CH_3$	$\rightarrow$	$R'CH_2CO_2H$	(91%)
RCH_2COCH_3	$\rightarrow$	$R'CH_2COCH_3$	(84%)
RCH_2OH	$\rightarrow$	$R'H$	(95%)
RCH_2CH_2OH	$\rightarrow$	$R'CH_3$	(77%)

This reaction provides a method for the synthesis of naphthalene derivatives on a preparative scale.

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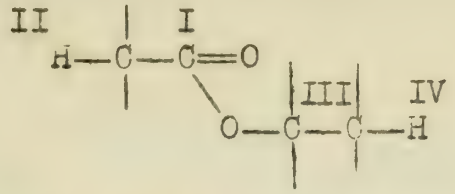
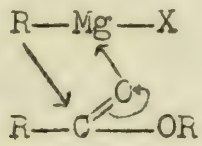
Reported by Roger Tull
April 23, 1948

REACTIONS OF CARBOXYLIC ESTERS WITH GRIGNARD REAGENTS

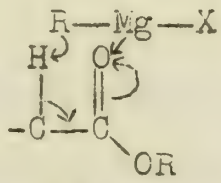


A strongly basic ion is capable of reacting with carboxylic esters at any of the four positions indicated: I, the carbonyl carbon, II, the α-hydrogen in the acyl portion, III, the α-carbon and IV, the β-hydrogen in the alkoxy portion (I).

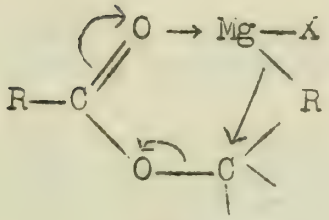
Grignard reagents, containing potentially the strongly basic alkyl or aryl anion, react at any of the four vulnerable positions of esters, resulting in four different types of reactions. The mechanism involves the probable coordination of the magnesium atoms of Grignard reagents with the carbonyl or alkoxy oxygen atoms of esters (2,3). The electron changes that may occur within the coordination complexes leading to the four types of reactions may be indicated as:



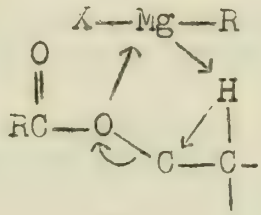
I



II



III



IV

Type I.--Addition occurs at the carbonyl carbon to form a ketone or more often a tertiary alcohol (4). Ethyl acetate and higher aliphatic homologs as well as ordinary aromatic esters such as ethyl benzoate exhibit mainly the carbonyl carbon reaction with most Grignard reagents. Whether the formation of tertiary alcohol involves a ketone as the intermediate or not is not clear yet.

1. $RCOOC_2H_5 + 2R'MgX + HOH \rightarrow RCR_2'OH + MgX(OH) + C_2H_5OMgX$

2. $RCOOC_2H_5 + R'MgX \rightarrow RCOR' + C_2H_5OMgX$

Type II.--An ester which has a relatively unreactive carbonyl carbon, or a relatively reactive α-hydrogen, is self-condensed by Grignard reagents to form a β-keto ester (acetoacetic ester conden-

sation). Complexity of the Grignard reagent increases the ease of self-condensation.

1. $2C_6H_5CH_2CO_2C_2H_5 \xrightarrow{(CH_3)_2CHMgBr} C_6H_5CH_2COCH(C_6H_5)CO_2C_2H_5 + C_2H_5OH$ 93% (5)

2. $2CH_3CO_2C(CH_3)_3 \xrightarrow{(CH_3)_2CHMgBr} CH_3COCH_2CO_2C(CH_3)_3 + (CH_3)_3COH$ 40-50% (5)

3. $C_3H_7CO_2C_2H_5 \xrightarrow{(CH_3)_3CMgCl} C_3H_7COCH(C_2H_5)CO_2C_2H_5$ 50% (6)

4. $i\text{-}C_5H_{11}CO_2C_2H_5 \xrightarrow{Mes\text{-}MgBr} i\text{-}C_5H_{11}COCH(i\text{-}C_4H_9)CO_2C_2H_5$ 51% (7)

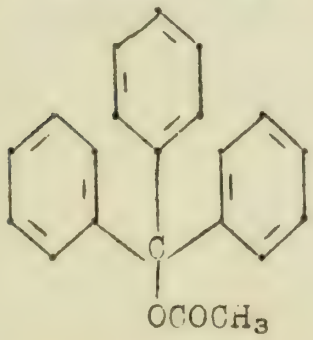
5. $n\text{-}C_4H_9CO_2C(CH_3)_3 \xrightarrow{(C_2H_5)_2NMgBr} n\text{-}C_4H_9COCH(C_3H_7)CO_2C(CH_3)_3$ 53% (8)

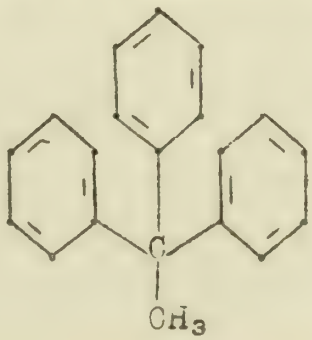
6. $(C_6H_5)_2CHCO_2C_2H_5 \xrightarrow{(CH_3)_2CHMgBr} [(C_6H_5)_2CO_2C_2H_5]MgBr \xrightarrow{C_6H_5COCl} C_6H_5COC(C_6H_5)_2CO_2C_2H_5$ (9)

Last case is unique. The magnesium derivative of an ester is condensed with a component other than the original ester.

Type III.--Substitution of the α-carbon in the alkoxy portion of esters has been observed with certain esters in which the carbonyl carbon is hindered and the α-carbon is attached to relatively strong electron releasing groups.

1. $RCO_2CH_2CH{=}CH_2 + R'MgX \rightarrow RCO_2MgX + R'CH_2CH{=}CH_2$ (10)

2. 

$\xrightarrow{CH_3MgBr}$


68% (11)

3. $C_6H_5CO_2C(C_6H_5)_3 + CH_3MgI \rightarrow (C_6H_5)_3CCH_3 + C_6H_5CO_2MgI$ (9)

Type IV.--β-Hydrogen in the alkoxy portion is removed, ac-

companied by the elimination of the carboxylate group to form an olefin (β-elimination). Reaction has been realized for the first time in the following instance in which the ester has a hindered carbonyl carbon and an activated β-hydrogen (9).

$$\text{Mes-}CO_2CH(C_6H_5)CH_2C_6H_5 + C_6H_5MgBr \rightarrow C_6H_5CH{=}CHC_6H_5 + \text{Mes-}CO_2MgBr \quad 80\text{-}90\%$$

With CH_3MgI or C_2H_4MgBr under similar conditions the result is different.

$$\text{Mes-}CO_2CH(C_6H_5)CH_2C_6H_5 + CH_3MgI \rightarrow \overset{\text{1,2,3,4-tetraphenylbutane}}{C_6H_5CH_2(C_6H_5)CHCH(C_6H_5)CH_2} \quad 8\text{-}9\%$$

$$+ C_6H_5CH{=}CHC_6H_5 + \text{Mes-}CO_2MgBr \quad 30\text{-}40\%$$

Mechanism of this type of reaction probably involves the α,β-diphenylethyl free radical as intermediate (12).

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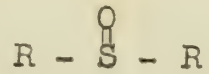
Reported by L. C. Chou
April 23, 1948

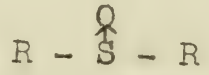
THE SULFUR-OXYGEN BOND IN SULFOXIDES AND SULFONES

In the early formulations of the higher oxides and oxy-acids of elements in Groups V, VI, and VII, the oxygen atoms attached to a central atom were supposed to be held by double bonds as in (I).



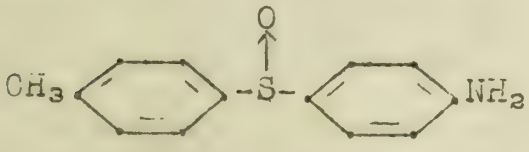
I

When, later, Lewis placed covalency on a physical basis by introducing the concept of electron sharing, he showed that it was possible to formulate many compounds, including the higher oxides and oxy-acids, with an octet of electrons around each atom (1). In place of the double bonds in the old formulations, he postulated single covalencies for which the central atom provides both shared electrons as in (II).

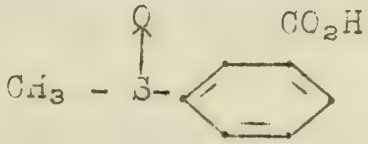


II

Application of Bohr's theory of atomic structure and later of wave mechanics to valency problems strongly supported this principle as applied to elements in the first short period (2). Observations on stereochemical properties of compounds of the type (III and IV)



III



IV

and the large electric moments of diphenylsulfoxide and diphenylsulfone (3) appeared to support the octet formulae for the oxy-compounds.

This view was challenged (4) when it was discovered by means of electron diffraction investigations that the bond lengths in the common oxy-acids are much shorter than single bonds should be, being in fact as short as double bonds or even shorter. On the basis of considerable evidence (5,6,7) true coördinate links appear to be nearly of the length to be expected for a normal, single covalency between the same two elements.

The extreme shortness of the sulfur-oxygen linkage, shorter than a triple bond, has been explained (4) as a result of resonance

with triple-bonded structure, e.g., $S \overleftarrow{=} O$, but a large contribution, such as is essential in this theory in most of the oxy-compounds examined, would reduce the moment of the sulfur-oxygen bond to zero, or even reverse it. No such drastic effect is observed; the bond is still decidedly polar.

On more careful examination, dipole moment data leave little doubt that the sulfur-oxygen bond is not a single bond. The moment for a true coördinate link 1.36 A° long, $N \rightarrow O$ in the amine oxides, would be 6.43 D. Actually it is about 4.38 D., i.e., 68% of theory. If the sulfur-oxygen bond was a coördinate link, its calculated moment would be 6.86 D. The actual value is, however, 2.5 D. (8), i.e., only about 35% of the theoretical value.

To make the evidence more complete it has been shown (9) that when sulfur forms a genuine coördinate link, as in (V)

$$(C_2H_5)_2S \rightarrow BCl_3$$

V

a much more highly polar bond is generated than is to be found in sulfoxides and sulfones.

Additional evidence is given (9) by the fact that the large heat of formation of the sulfur-oxygen link leaves little doubt that it is stronger than it would be if it were a coördinate link.

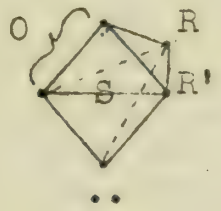
The possibility of a resonance hybrid of the coördinate and the double bond is ruled out by the development of the theory of resonance which makes clear the necessity for avoiding the possibility of resonance of the coördinate link with other bond types, e.g., with the double bond.

Having decided what this bond is not, consideration must be given as to what it is. Two arguments have been advanced against the double bond formulations: one is that the sulfur-oxygen bond does not undergo addition reactions, i.e., does not add water, Grignard reagents, etc. The other is that stereochemical properties of compounds of the type (III and IV) seem to be strong evidence against the sulfur-oxygen bond being double.

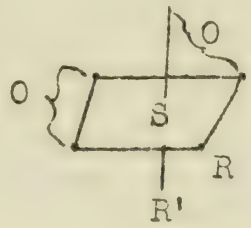
The first argument is answered as follows: Data on heats of formation indicate that for elements of variable valence, single bonds formed in going from the lower to the higher covalency are weaker than those formed with the lower valency. This phenomenon is thought to be due to steric effects. Therefore, addition reactions do not occur because of the relative weakness of these "additional" single bonds formed in the breaking of the double bond.

The non-planar configuration of the sulfur-oxygen link can no

longer be regarded as decisive evidence against the bond being double. The molecule of a sulfoxide may be represented as in (VI) (10), that of a sulfone as in figure (VII).



VI



VII

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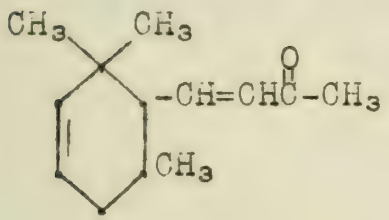
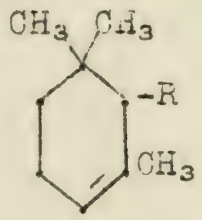
April 23, 1948

THE CHEMISTRY OF THE VIOLET ODOR: THE SYNTHESIS OF dl-α-IRONE

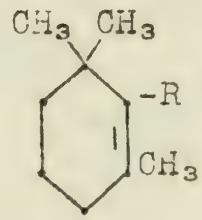
In 1893 Tiemann and Krüger (1), investigating the odoriferous principle of the violet, isolated an active substance to which they gave the name irone. Further research resulted in a better yield of the odorous component from orris-root, the dried rhizomes of *Iris florentina*. Tiemann and Krüger arrived at the empirical formula $C_{13}H_{20}O$ and proposed structure (I) for irone. Attempts at synthesis did not yield the desired product, however; instead, α- and β-ionone were obtained. This failure has permitted the development of the chemistry of the carotenoid substances and the knowledge and synthesis of Vitamin A.



I



α-ionone

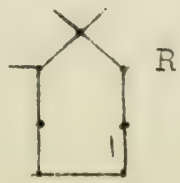


β-ionone

(R = $-CH=CHC(=O)-CH_3$)

In 1933 Ruzicka and coworkers, unable to explain differences between tetrahydroirone and tetrahydroionone on a stereochemical basis alone, showed that irone really has the composition $C_{14}H_{22}O$, an empirical formula suggesting a methylionone (2). Dehydration of irone yielded the hydrocarbon, irene, $C_{14}H_{20}$, for which these workers postulated formula (II), a structure later proved by independent synthesis (3). On this evidence irone might be presumed to be a 6-methylionone. Ozonolysis and chromic acid oxidation of irone, however, yielded 2,2,3-trimethylpimelic acid, which could not be explained on the basis of a six-membered ring. Similar studies on dihydroirane obtained by Wolff-Kishner reduction of the natural product led to the postulation, which was widely accepted, of structure (III) (4). In addition, investigation of absorption spectra and physical properties brought about the realization of isomeric α- and β-irones (IIIα and IIIβ), respectively similar to α- and β-ionone, in the product as extracted commercially from orris-root (5,6).

II



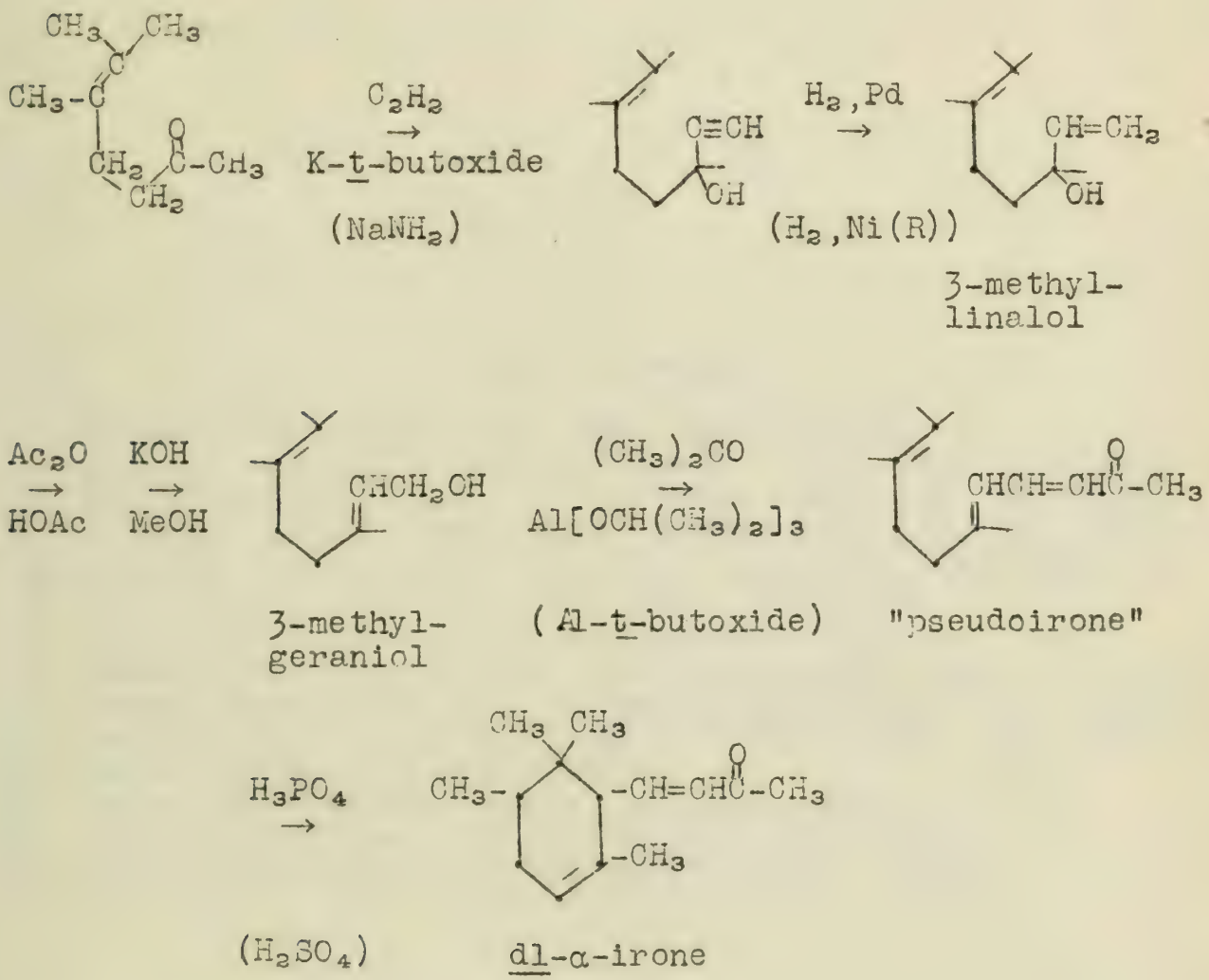
IIIα

20% $\xrightarrow{H_2SO_4}$

IIIβ

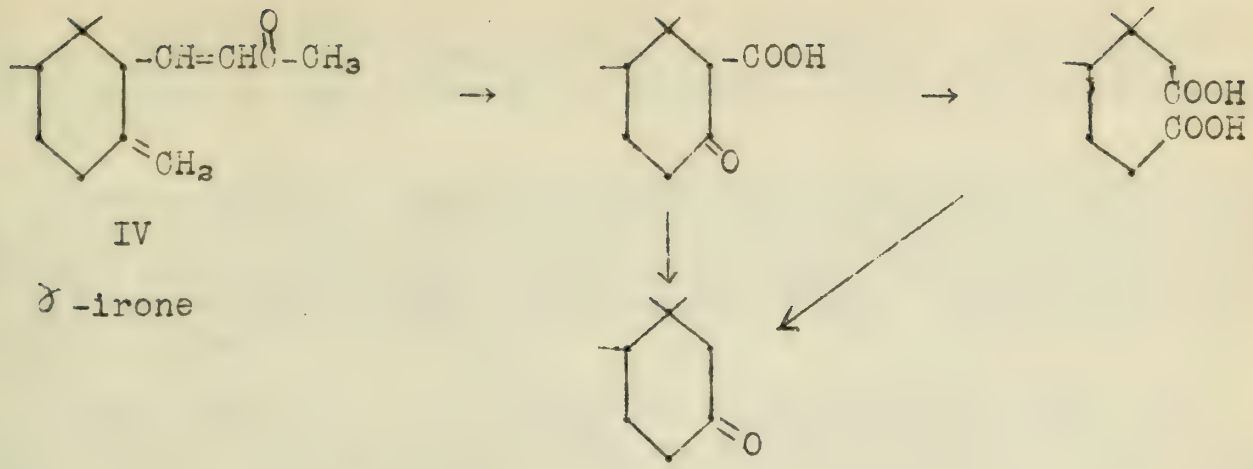
III

A ketone similar to (III) was synthesized by Stoll and Scherrer (7), but it did not have the irone odor. The problem has recently been crystallized, however, by the successful synthesis by Ruzicka and coworkers (8), and independently by Naves (9), of an α-irone identical in physical properties with the major fraction of the natural product. This compound, dl-6-methyl-α-ionone, was prepared according to the following scheme:



The Naves plan of synthesis was identical. Differences in the reagents used to effect the same stepwise transformations shown above are indicated in parentheses.

The six-membered ring structure for α-irone was justified by Ruzicka on the basis of the presence in natural irone of a γ-form (IV). The existence of this form was suspected and later proved by the production of considerable amounts of formaldehyde on ozonolysis of the natural product. The isolation of the 2,2,3-trimethylpimelic acid can be explained by acid cleavage of the normal oxidation product of (IV), 2-carboxy-3,3,4-trimethylcyclohexanone. A side-reaction to be expected was ketone cleavage of this product, yielding 3,3,4-trimethylcyclohexanone. This ketone was also isolated and shown to be identical with the compound obtained by cyclization of the substituted pimelic acid (10).



IV

γ-irone

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Reported by Herbert S. Elins
April 30, 1948

REACTIONS OF ACROLEIN

I. Introduction.--Acrolein is a colorless, volatile liquid with a characteristic pungent odor and lachrymatory effect. It is the simplest of the unsaturated aldehydes and has long been known to chemists.

Pharmacological investigations have shown that: (1) Acrolein is toxic, the vapors acting principally on the mucous membrane of the eyes and respiratory tract and (2) the concentration tolerable to man due to its extreme lachrymatory effect is far below the minimum lethal concentration.

Since there are two functional groups in acrolein, it possesses remarkable versatility as an intermediate in the synthetic field. The fact that these functional groups are conjugated further enhances the reactivity of the compound. This extreme reactivity requires that caution be exercised in using it under unfamiliar conditions, since some reactions may proceed with almost explosive violence. The formation of polymers occurs readily, thus interfering with many reactions. However, if one adds acrolein portionwise to the reaction system, the polymer forming tendency is lessened and the probability of accomplishing the desired reaction is increased.

II. Reactions.--

A. Halogens normally add across the double bond.
   1. Acrolein + X_2 → $XCH_2CHXCHO$
   2. The α-halo-acrolein has been reported also, formed through direct halogenation (1).

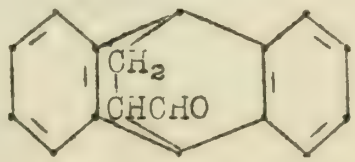
B. Halogen acids add 1,4-. This is less general than X_2 addition.
   1. Acrolein + HCl → $ClCH_2CH_2CHO$ (2,3).

C. Grignard reagents add 1,2-.
   1. Acrolein + Grignard Reagent → Corresponding aliphatic or aryl vinyl alcohols (4,5).

D. HCN and acetic anhydride add 1,2- (6,7).
   1. Acrolein + HCN → Acrolein cyanohydrin
   2. Acrolein + Ac_2O → Acrolein diacetate

E. Malonic acid adds 1,2-, in an aldol type reaction (8,9).
   1. Acrolein + $CH_2(COOH)_2$ → β-vinylacrylic acid

F. Conjugated dienes yield the usual Diels-Alder condensation products. This reaction proceeds readily (10,11,12,13).
   1. Acrolein + Anthracene →



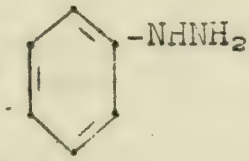
G. Ammonia yields a variety of products depending on conditions and reagents.
   1. Acrolein + NH_3 in aq. soln. → acrolein-ammonia polymer (14)

2. Acrolein + NH_3 in presence of acetaldehyde over Al_2O_3 → pyridine (15)
3. Acrolein + NH_3 in vapor phase over $AlPO_4$ → α- and β-picoline (17)

H. Secondary aliphatic amines yield unsaturated diamino compounds.

1. Acrolein + $2(CH_3)_2NH$ → $(CH_3)_2NCH_2CH{=}CHN(CH_3)_2$ (18)
2. Acrolein + $2(CH_3)_2NH$ $\xrightarrow{HCN}$ $(CH_3)_2NCH_2CH_2CHN(CH_3)_2$ (18)
   CN

I. Phenylhydrazine yields the substituted pyrazoline.

1. Acrolein + 

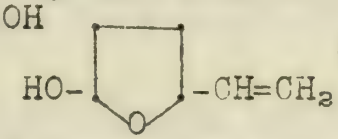
→ 

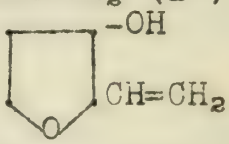
J. The reactions of methanol or ethanol in the presence of HCl result in a mixture of products representing almost every possible combination of reactions of the alcohol and HCl with the double bond and carbonyl group. Amounts obtained vary with relative quantities of reactants.

K. Oxidation products are dependent on the conditions of the reaction.

1. Acrolein in the presence of air → polymers
2. Acrolein in the presence of $NaClO_3$-OsO_4 → glyceraldehyde (19).
3. Acrolein by patented processes → acrylic acid

L. Reduction and/or hydrogenation give a variety of products, depending on the catalyst.

1. Acrolein $\xrightarrow{H_2\text{-}Ni}$ CH_3CH_2CHO + $CH_3CH_2CH_2OH$
2. Acrolein $\xrightarrow{Zn\text{-}Cu}$ $CH_2{=}CHCH(OH)CH(OH)CH{=}CH_2$ (20)
3. Acrolein $\xrightarrow{Mg\text{-}CH_3COOH}$ 

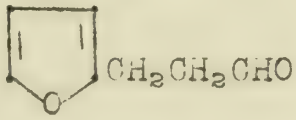
+ 

(21,22

M. $NaHSO_3$ and PCl_5 react with both functional groups.

1. Acrolein + $NaHSO_3$ → $NaO_3SCH_2CH_2CH(OH)SO_3Na$
2. Acrolein + PCl_5 → $ClCH_2CH_2CHCl_2$ + $ClCH{=}CHCH_2Cl$ + $CH_2{=}CHCHCl_2$ (23).

N. Miscellaneous C-C condensations.

1. Acrolein + Furan → 

+

(24)

2. Acrolein + Phenylacetaldehyde → 

(25)
3. Acrolein + HCHO → Pentaerythritol (26)
4. Acrolein + Phenanthrene → Perylene (27)

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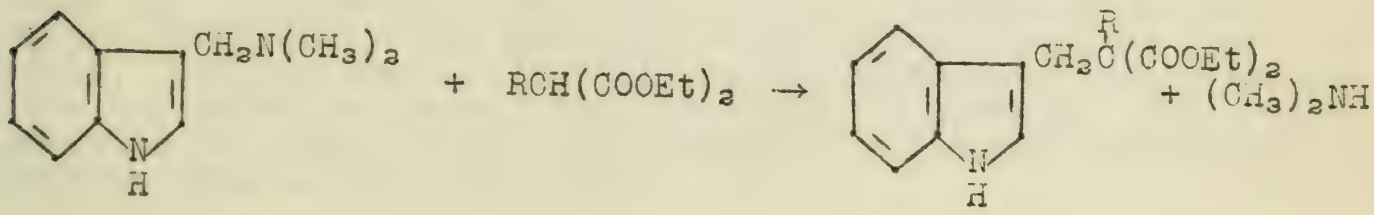
Eighty-seven additional references available in Report No. S-9941 on ACROLEIN by Shell Development Company, January 6, 1947.

Reported by A. H. Anderegg
April 30, 1948

ALKYLATIONS WITH NON-KETONIC MANNICH BASES

Several years ago it was reported that gramine (3-dimethylaminomethylindole) or a quaternary salt of gramine could be used to alkylate malonic esters. Since that time it has been shown that various substituted acetic esters as well as certain nitroparaffins undergo the same type of reaction with gramine. Recently dialkylaminomethylpyrroles and aminothiazoles have been employed as alkylating agents for malonic esters.

Gramine, which is readily prepared from indole, formaldehyde, and dimethylamine in the presence of acetic acid, alkylates malonic esters according to the general reaction (1-6):

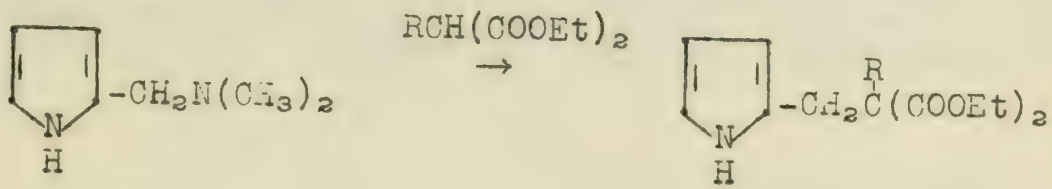


I II

R = H, $NHCOCH_3$, NHCOØ, NO_2

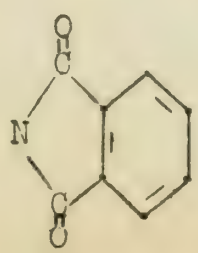
Three different sets of conditions have been employed to effect this reaction: (a) by heating the reagents in refluxing toluene or xylene in the presence of a basic catalyst (3), (b) by heating the quaternary salt of gramine with the sodiomalonic ester in an inert solvent such as dioxane or dibutyl ether (4), and (c) by the slow addition of excess dimethyl sulfate to a warm solution of gramine and the sodiomalonic ester (5). When acetamidomalonic ester is used, the yields for the three procedures are 90, 70, and 95% respectively.

However, when 2-dimethylaminomethylpyrrole was substituted for gramine and the reaction carried out as in (a) with acetamidomalonic ester, the expected ethyl α-acetamido-β-(2-pyrrole)-propionate (III, R = $NHCOCH_3$) was not obtained, but a good yield of a

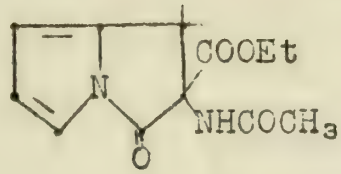


III

R = H, $NHCOCH_3$,



product to which the lactam structure (IV) was assigned was isolated (7).



IV

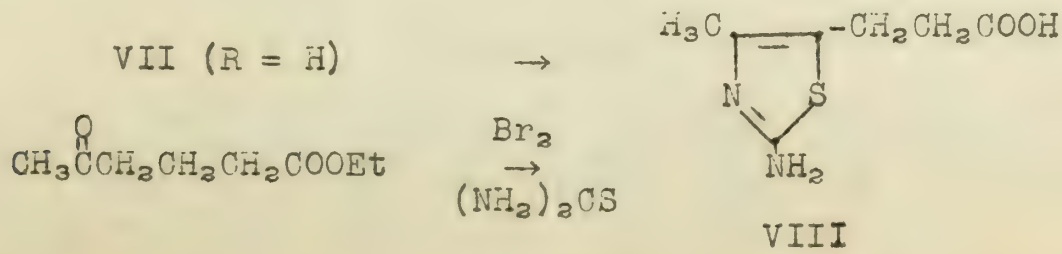
Under the experimental conditions of (b), 2-dimethylaminomethylpyrrole methiodide also gave the lactam IV, although in lower yield. The expected ester (III) was obtained when dimethyl sulfate was added to the malonic ester and the pyrrole. It is also possible to replace both amino groups of a 2,5-bis-aminomethylpyrrole with malonic ester (8).

Malonic esters have also been alkylated with acetamidothiazoles (8). For example, 5-dimethylaminomethyl-2-acetamido-4-methylthiazole (VI) in the form of its methyl sulfate gave diethyl 5-(2-acetamido-4-methylthiazylmethyl)-acetamidomalonate (VII, R = $NHCOCH_3$).

VI VII

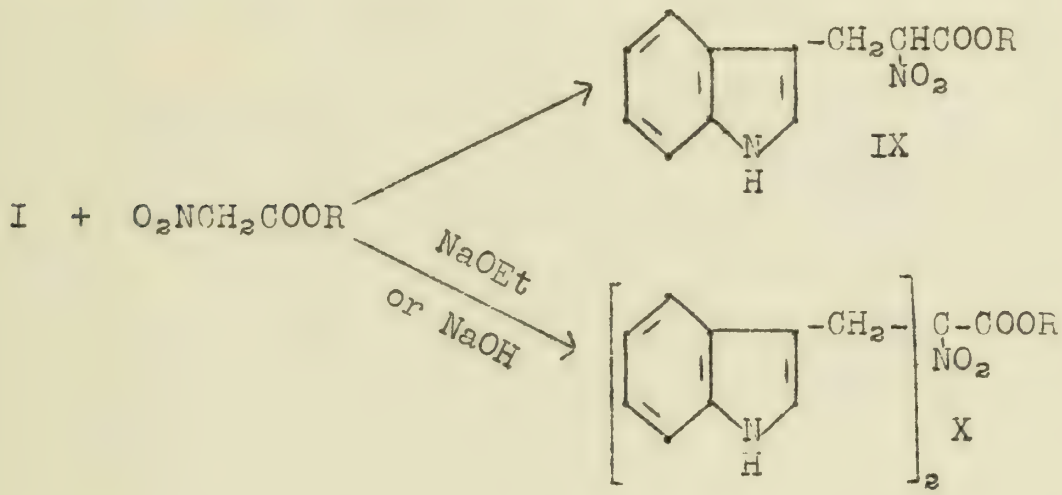
R = H, $NHCOCH_3$

Proof that alkylation had taken place in the ring was obtained by decarboxylation of compound VII (R = H) to the propionic acid VIII, which was identical with that synthesized by the interaction of ethyl γ-acetobutyrate, bromine and thiourea, and subsequent hydrolysis.



VIII

Several substituted acetic esters also have been alkylated by these bases. Gramine has been used to alkylate ethyl cyanoacetate (1), ethyl acetamidocyanoacetate (9), acetoacetic ester (1), and ethyl α-acetamidoacetoacetate (10); 2-dimethylaminomethylpyrrole has been used in the alkylation of ethyl cyanoacetate (both active hydrogen atoms were replaced by pyrrolemethyl radicals) and of ethyl acetamidocyanoacetate (7). Esters of nitroacetic acid are readily alkylated by gramine to yield esters of α-nitro-β-(3-indole)-propionic acid (IX). The product is obtained in good yield when the two reactants are heated in xylene in the absence of a catalyst (11). When the reaction is carried out in the presence of a basic catalyst, with or without an inert solvent, the ester of nitro-bis-(3-methylindole)acetic acid (X) is obtained (11,12).



Aliphatic nitro compounds are similarly alkylated by gramine, the dialkyl derivative being formed in the case of nitromethane (12).

Attempts to alkylate diketopiperazine (3) and hydantoin (3,7) with gramine have been unsuccessful.

Since the esters in which R is an amide or a nitro group may be converted to the amino compound readily, these alkylated products provide a convenient route to the corresponding amino acids. Furthermore, as the number of Mannich bases of this type prepared increases (13) the alkylation reaction may prove to be a general one.

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Reported by Jean V. Crawford
April 30, 1948

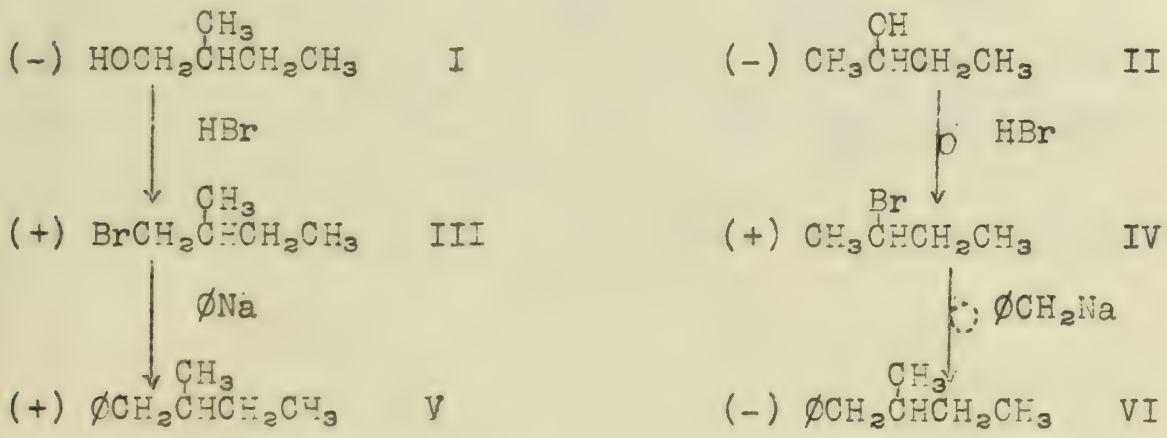
THE PREPARATION OF OPTICALLY ACTIVE HYDROCARBONS BY THE WURTZ REACTION

It has long been known that optically active hydrocarbons can be prepared by the Wurtz reaction if the reaction does not take place at the site of the asymmetric carbon atom (1). In more recent years, there have been reports of investigations in which the reaction proceeded at the asymmetric center, and three workers have reported reactions in which the products were optically active.

In 1928, Ott (2) reported the isolation of optically active 2,3-diphenylbutane in 22% yield from the products of the reaction between sodium and α-phenylethyl chloride. Brink, Lane, and Wallis (3) later reported a 25% yield of extensively racemized 3-methylnonane from the treatment of 2-bromooctane with ethyl sodium.

In January of this year, Letsinger (4) reported that he had obtained the <u>dextro</u> and <u>levo</u> forms of 1-phenyl-2-methyloctane and the <u>levo</u> form of 1-phenyl-2-methylbutane by methods involving the Wurtz reaction. These compounds were obtained in good yield and, in the case of at least the last compound mentioned, retained a considerable degree of optical purity. Letsinger estimated that the <u>levo</u> 1-phenyl-2-methylbutane was 26% racemized. Since no independent value for the rotation of 1-phenyl-2-methyloctane was available, he was not able to estimate the extent of racemization with the other two compounds.

Letsinger proposed that the reaction of the benzyl sodium with the secondary bromide took place with inversion; the main body of evidence which supports this postulate can be summarized as follows:



(-)I corresponds configurationally to (+)III and to (+)V (4,5) and (+)II corresponds to (+)IV (7,8,9). Accordingly, if (-)I corresponds to (+)II, the IV-VI conversion takes place by inversion. The postulate demands that (-)I and (-)II be configurational enantiomorphs, and this fact has not been demonstrated with absolute certainty. In support of this relationship, the following

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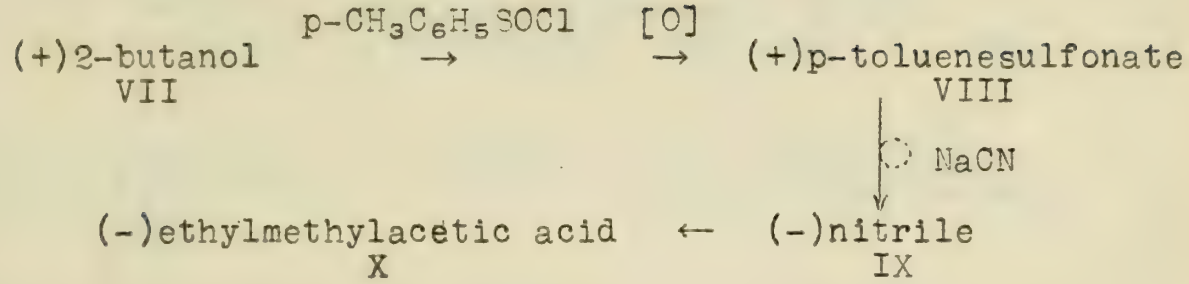
facts may be noted (10,11,5):



(+)ethylmethylacetic acid → ester → (-)2-methyl-1-butanol

The doubtful reaction in this series is the conversion of VIII to IX, which has been postulated to occur by inversion (10). The occurrence of the inversion at this point has not been finally demonstrated, having been proved by analogy only.

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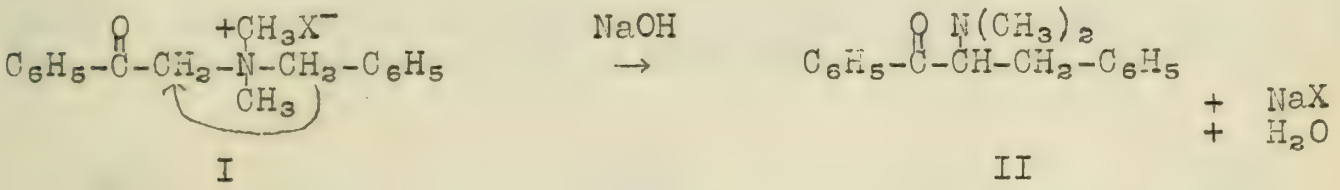
Reported by Richard H. Tennyson
May 7, 1948

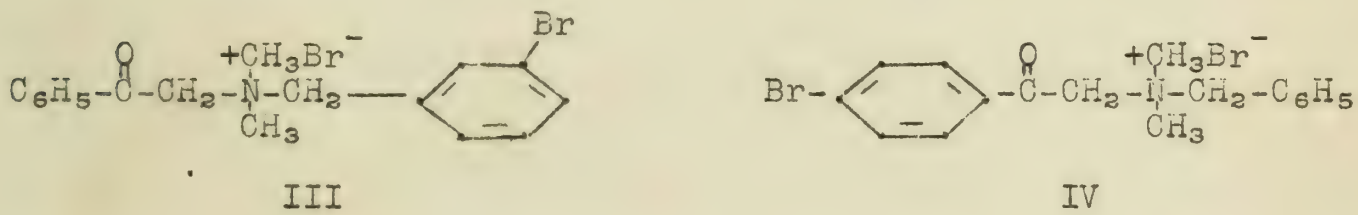
REARRANGEMENT OF CERTAIN QUATERNARY AMMONIUM SALTS

Stevens and coworkers (1) found that the rearrangement I → II, involving the shift of a benzyl group from the quaternary nitrogen atom to the methylene group of the phenacyl radical, took place almost quantitatively by treatment of the salt, I, with alkali.



Upon further investigation (2-8), they found that replacement of the phenacyl or benzyl radicals by certain other groups would not prevent the reaction, and that a sulfonium salt of similar structure would undergo the rearrangement.

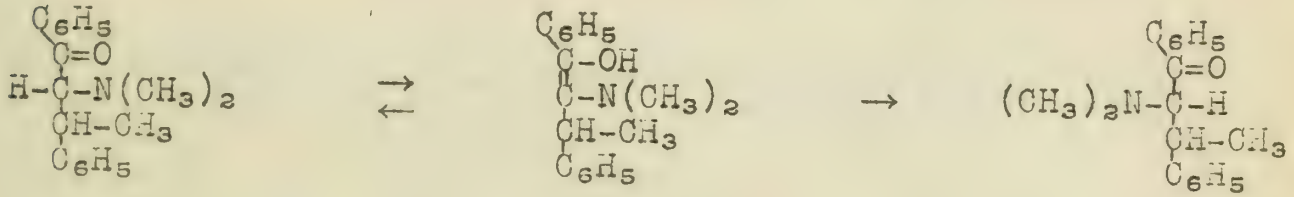
The reaction was determined to be intramolecular (2) by rearranging a mixture of the salts III and IV, which have similar



rates of rearrangement. From this mixed rearrangement, only the rearrangement products corresponding to the individual salts were isolated. Stevens postulated the mechanism of the reaction to be through an intermediate benzyl anion (2), and this mechanism was supported by the fact that substitution on the benzyl radical of a negative group, such as the nitro group, which would tend to stabilize the benzyl anion, materially accelerated the rearrangement (4). The general observation was that the presence of electron-withdrawing groups on the benzene ring of the benzyl radical accelerated the reaction, while their presence on the benzene ring of the phenacyl radical retarded it.

To confirm the fact that the rearrangement is intramolecular, Kenyon and coworkers (9) recently ran the rearrangement V → VI, using the optically active salt, V, in which the migratory radical is attached to the rest of the molecule by an asymmetric carbon

atom, and found that they obtained the two expected diastereoisomers which they termed the α- and β- forms, in almost optically pure state. Stevens had previously rearranged the racemic salt V, and found that the two racemic rearrangement products were formed in almost equal amount. On heating the β- form of VI in alkaline medium, it is converted almost completely to the α- form. Stevens suggested that this conversion was an epimerization due to enolization. This affords an example of an asymmetric transformation under the influence of an optically active center. Had the conversion of enol



β- form α- form

to keto form followed its normal course, an equilibrium mixture of the two diasteroisomers would have resulted.

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Reported by Donald L. Felley
May 7, 1948

RECENT APPLICATIONS OF CYANOETHYLATION

This report deals with reactions of acrylonitrile, exclusive of polymerization, which have been described in the literature since the seminar report by J. E. Mahan (1).

Reactions with Alcohols.--In 1943 Koelsch prepared β-ethoxypropionitrile by the reaction of ethyl alcohol with acrylonitrile (2). Later it was shown that all aliphatic alcohols of the range C_1 to C_{10} could be treated with acrylonitrile to give the corresponding β-alkoxynitriles in excellent yields (3). For example:

$$N\text{-}C_8H_{17}OH + CH_2{=}CHCN \xrightarrow{Na} C_8H_{17}OCH_2CH_2CN \quad (80\%)$$

I

With alcohols containing primary and secondary amino groups, acrylonitrile yields N-cyanoethylation products (4). However, with tertiary amino alcohols, it is possible to cause the hydroxyl group to add to the unsaturation in the nitrile giving dialkylamino alkoxypropionitriles (5).

$$R_2NCH_2CH_2OH + CH_2{=}CHCN \xrightarrow{NaOCH_3} R_2NCH_2CH_2OCH_2CH_2CN$$

II

Reactions with Aldehydes.--According to the patent literature, formaldehyde can be made to react with acrylonitrile in aqueous medium to yield the formal or hemiformal of ethylene cyanohydrin (6). The products obtained are used as intermediates for plasticizers and resins.

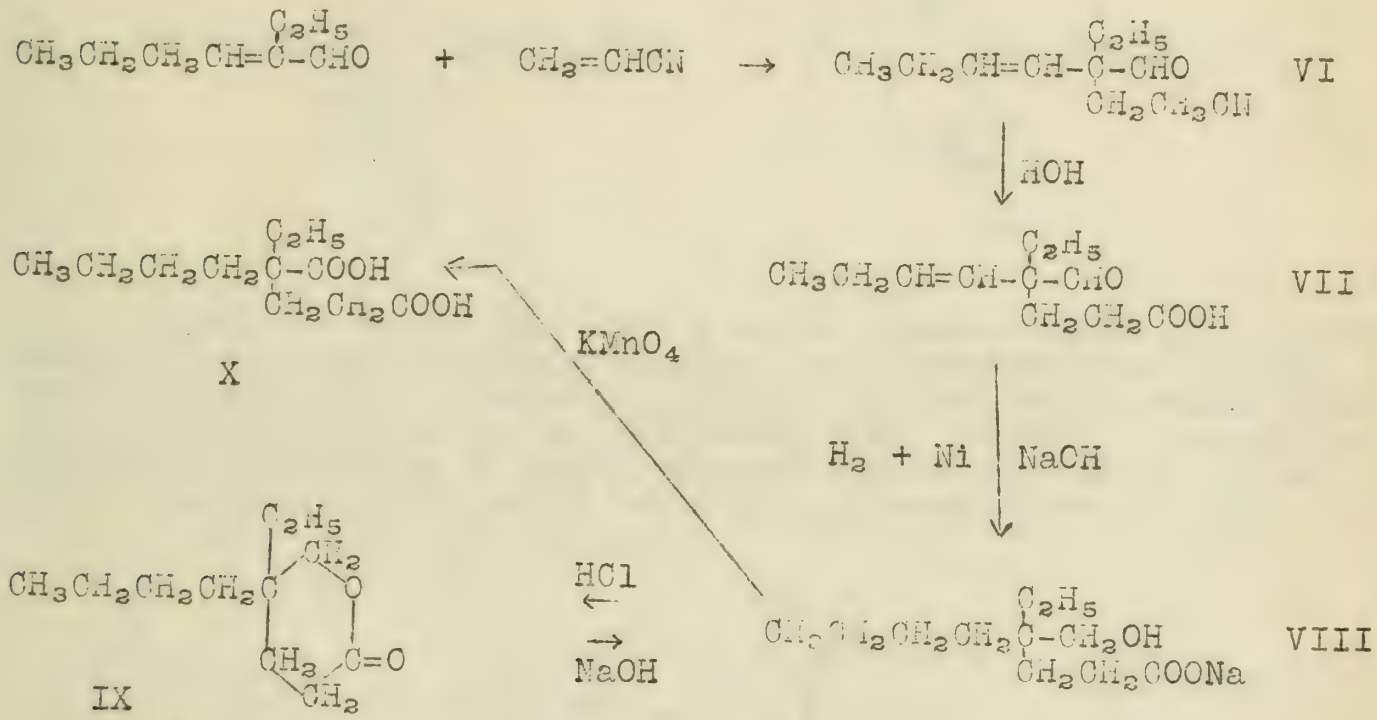
$$CH_2O + CH_2{=}CHCN \xrightarrow{H_2O} HOCH_2OCH_2CH_2CN \xrightarrow{CH_2=CHCN} CH_2(OCH_2CH_2CN)_2$$

III IV

Bruson has indicated that in general aldehydes, unlike ketones, react with acrylonitrile to yield complex condensation products. However, he has shown that direct cyanoethylation will take place with α-hydrogen bearing aldehydes which do not readily aldolize, oxidize or resinify under the influence of alkaline catalysts (7). Typical of such aldehydes are the dialkyl acetaldehydes, particularly those higher in the series than isobutyraldehyde. Thus:

V

α,β-Unsaturated aldehydes of the type α-ethyl-β-propyl acrolein which lack an α-hydrogen atom undergo a 1,3-hydrogen shift to yield the α-cyanoethylated derivatives (7,9). This was shown to take place by the following sequence of reactions:



Reactions with Haloforms.--Since the haloforms possess labile hydrogen atoms, they add to acrylonitrile to yield trihalobutyronitriles.

$$X_3CH + CH_2{=}CHCN \xrightarrow{\text{"TRITON B"}} X_3CCH_2CH_2CN \quad XI$$

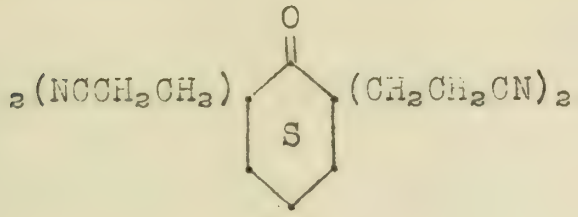
The products, X, were found to have use as insecticides; their structure was proven by conversion to the corresponding acids and amides. This reaction offers a simple method of preparation for these otherwise inaccessible compounds (9).

While chloroform and bromoform condensed with the nitrile, iodoform did not behave similarly. In the presence of "Triton B", iodoform failed to react with acrylonitrile and instead yielded an addition product of the haloform and the quaternary hydroxide.

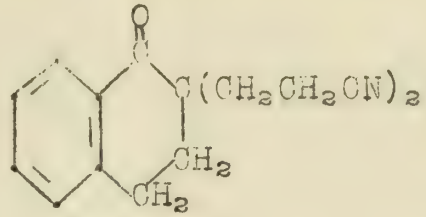
$$\underset{\text{"Triton B"}}{[C_6H_5CH_2N(CH_3)_3]^+OH^-} + CHI_3 \rightarrow \underset{XII}{C_6H_5CH_2N(CH_3)_3I\cdot CHI_3}$$

Reactions with Cyclic Ketones.--Cyclic ketones may be mono-, di-, tri- or tetra-cyanoethylated depending upon the substitution

on the atoms adjacent to the carbonyl group (10). Thus cyclohexanone is tetracyanoethylated while α-tetralone adds two cyanoethyl groups.

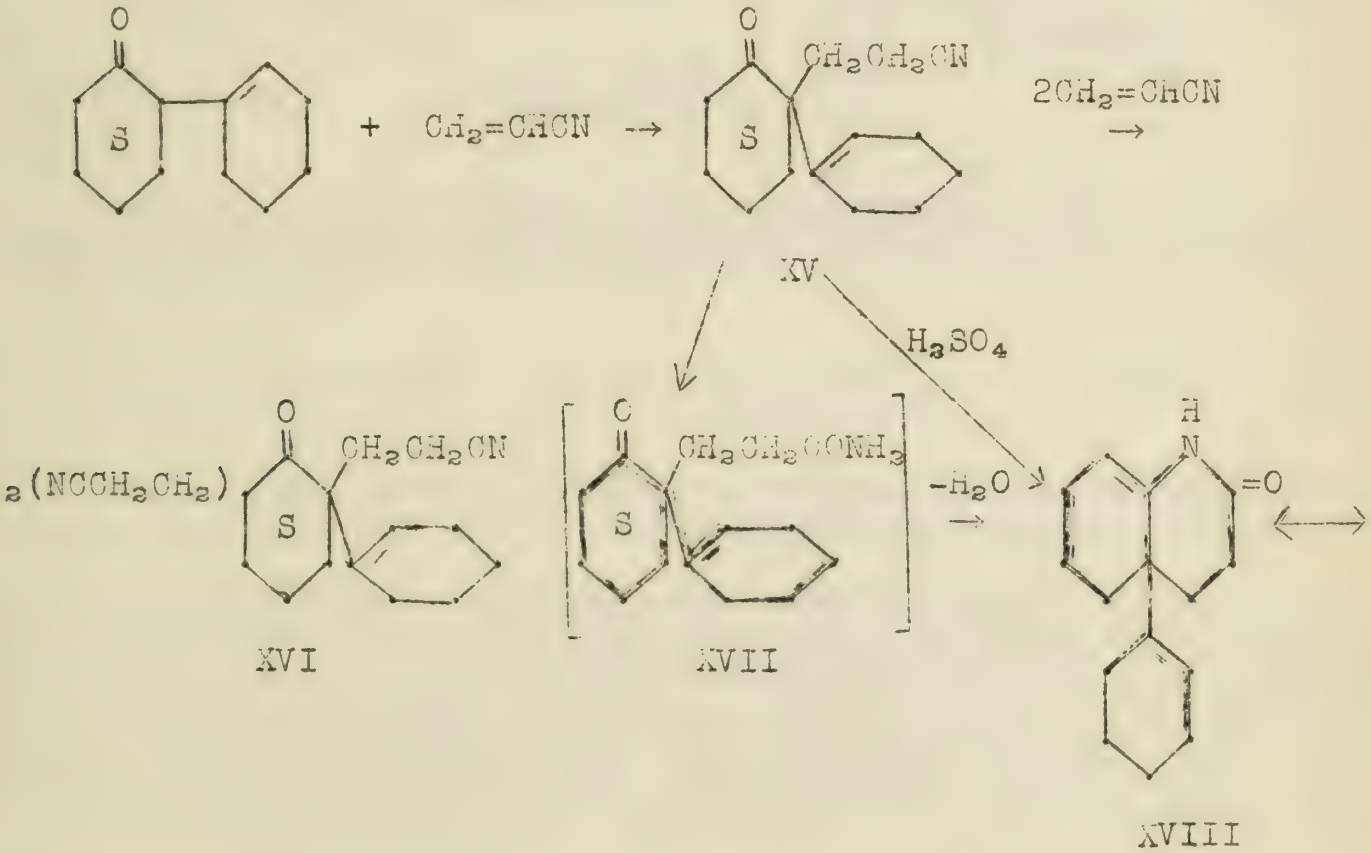


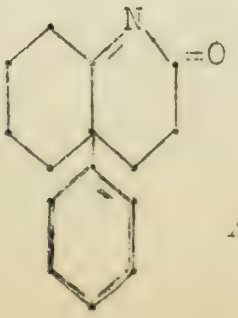
XIII



XIV

Bruson has shown (11) that with an α-substituted cyclic ketone such as 2-cyanohexenylcyclohexanone, monocyanoethylation first occurs largely on the methenyl group. Further condensation with acrylonitrile yields the tricyanoethylation product. Bruson found that acid hydrolysis of the monocyanoethylation product did not yield the anticipated amide but a hexahydroquinolone instead.





XIX

Reactions with Sulfones and Sulfonamides.--When the cyanoethylation reaction was applied to an active methylene sulfone, two β-cyanoethyl groups were introduced on the methylene C atom (11). For example:

$$C_6H_5CH_2SO_2C_6H_5 + CH_2{=}CHCN \xrightarrow{\text{"TRITON B"}} C_6H_5{-}C(CH_2CH_2CN)_2{-}SO_2C_6H_5 \quad \text{XX}$$

In an earlier paper (12), Bruson reported that the cyanoethylation of a sulfonamide introduced two cyanoethyl groups on the methylene C atom. A recent reinvestigation of the reaction indicates that the two cyanoethyl groups are attached to the N atom of the sulfonamide (11). This was proven through synthesis of the cyanoethyl derivative by another route.

$$C_6H_5CH_2SO_2NH_2 + 2CH_2{=}CHCN \rightarrow C_6H_5CH_2SO_2N(CH_2CH_2CN)_2 \quad \text{XXI}$$

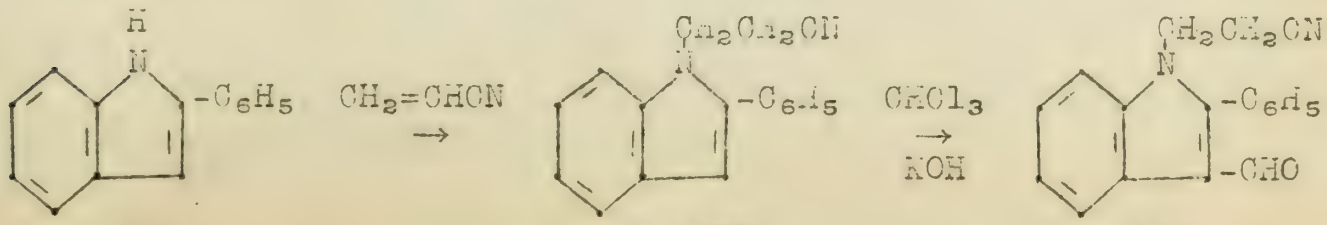
$$C_6H_5CH_2SO_2Cl + HN(CH_2CH_2CN)_2 \rightarrow C_6H_5CH_2SO_2N(CH_2CH_2CN)_2$$

Reactions with Certain Active H Compounds.--Like primary amines, arsines also readily undergo cyanoethylation to furnish tertiary arsines (13).

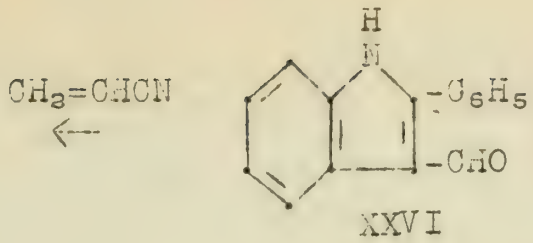
$$RAsH_2 + 2CH_2{=}CHCN \rightarrow RAs(CH_2CH_2CN)_2 \quad \text{XXII}$$

These β-cyanoethyl arsines are of therapeutic interest and may easily be converted to the corresponding amidines and amidine salts.

In substituted compounds containing NH in a heterocyclic linkage, active positions other than amino or imino might undergo cyanoethylation. In an effort to determine whether C- or N-cyanoethylation takes place in 2-phenylindole, 2-phenylindole-3-aldehyde was treated with acrylonitrile, and the cyanoethyl derivative of 2-phenylindole was formylated. The products obtained were found to be identical showing that cyanoethylation occurs on the N-atom of 2-phenylindole (14).



XXIII XXIV XXV



XXVI

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Reported by H. Rosenberg
May 7, 1948

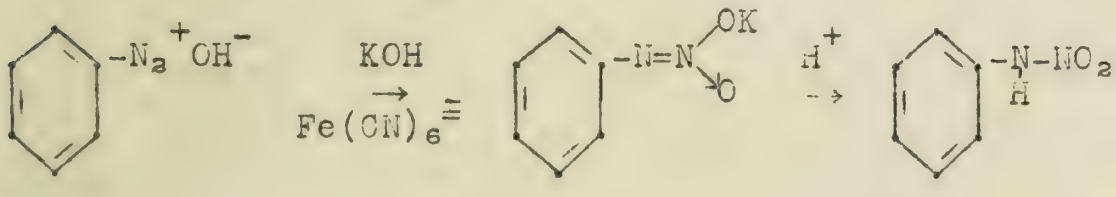
THE CATALYZED NITRATION OF AMINES

It is interesting to note that the first nitramine prepared and recognized as such is still one of the most important and widely known representatives of this class of compounds. In 1877 Mertens isolated a new compound from the nitration of dimethyl aniline. It remained for Van Romburgh, six years later, to characterize this compound as picrylmethylnitramine, familiar to us as tetryl. Within days, Franchimont prepared oxalyl-bis-methylnitramide and dimethylnitramine. These discoveries led to extensive research in the field, and a variety of preparative methods for nitramines was developed.

The usual nitrating agents (nitric acid, nitric acid-sulfuric acid, nitric acid-acetic anhydride) are in general not applicable to the direct nitration of amines. Primary nitramines are not available by direct nitration, but secondary nitramides are more readily available by this method and their ammonolysis thus affords a convenient route to primary nitramines:

$$RNH_2 \xrightarrow{Ac_2O} RNH\text{-}Ac \xrightarrow{HNO_3} R\text{-}\underset{Ac}{N}\text{-}NO_2 \xrightarrow{NH_3} RNH\text{-}NO_2 + AcNH_2$$

Bamberger, investigating oxidation of diazonium hydroxides, prepared the first aryl primary nitramines. He gave the name diazobenzolic acid to the product isolated from the oxidation of benzene diazonium hydroxide. This proved to be phenylnitramine:



(80% yield)

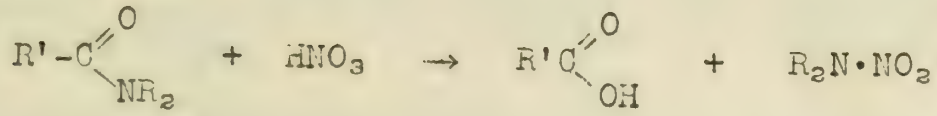
Primary nitramines may also be obtained, in poor yield, by treatment of a chloramine with silver nitrite:

$$RNH{\cdot}Cl + AgNO_2 \rightarrow RNH{\cdot}NO_2 + AgCl$$

If available, the corresponding primary nitrosoamine may be oxidized to yield a primary nitramine. Suitable oxidizing agents are permanganate and nitric acid. Yields are generally low.

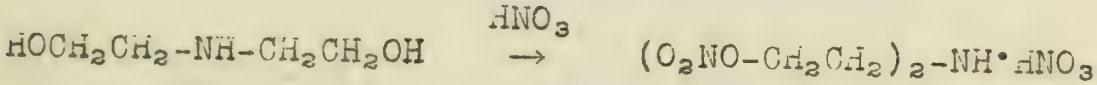
The preparation of secondary nitramines, $R_2N\text{-}NO_2$, is somewhat easier than that of primary nitramines, but most methods to date have not been entirely satisfactory. It was noted by early workers that negatively substituted secondary amines, for example, imino-bis-acetonitrile, could be nitrated directly. Unsubstituted secondary amines must be prepared indirectly. A con-

venient route is the treatment of disubstituted amides with nitric acid:



The early work in the field, including the above methods and several others of very limited applicability, has been thoroughly reviewed in reference (1). In spite of predominance of poor yields from the methods available, a great variety of nitramines was prepared and investigated in the two decades following Van Romburgh's work.

Wartime research at the University of Toronto by Wright et al (2-5) led to the suggestion that dinitroxydiethylnitramine might prove an excellent explosive comparable tp PETN. The nitrate salt of dinitroxydiethylamine was readily prepared by treating diethanolamine with 100% nitric acid (2):



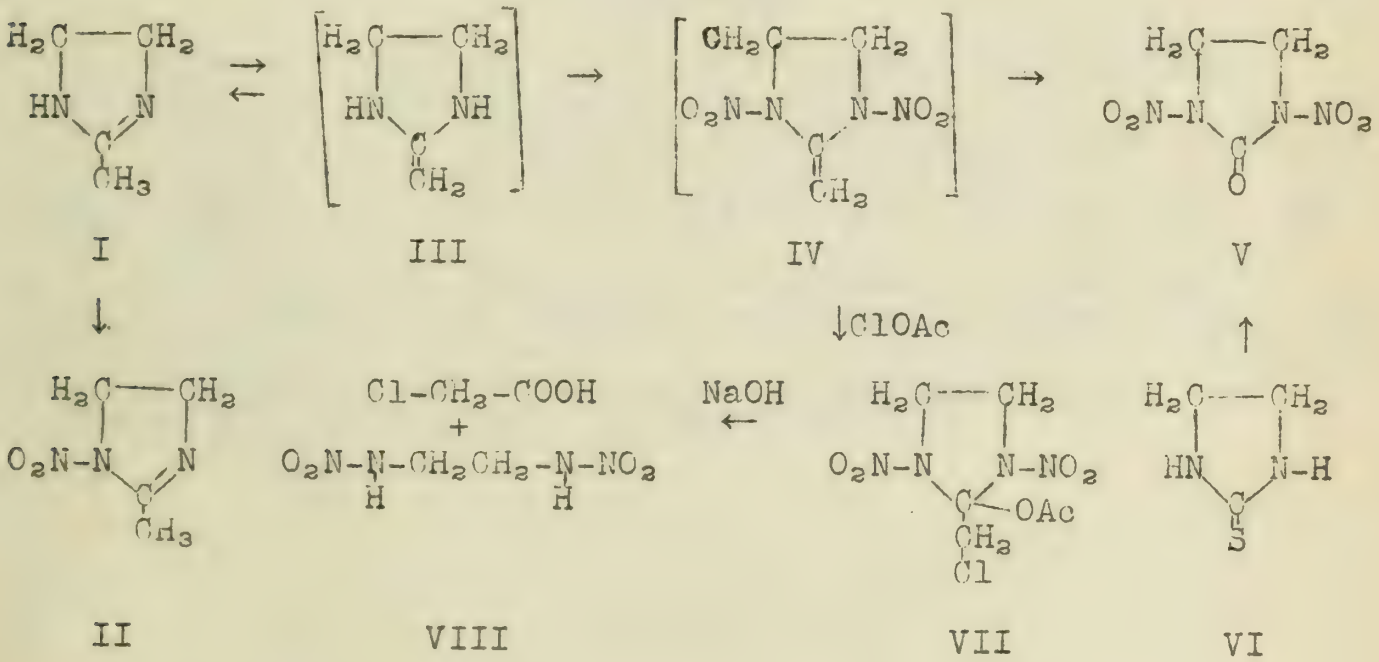
Attempts to prepare the nitramine from this compound by previously known methods gave only poor results, until the fortuitous discovery that a sample of the salt which had been in a desiccator over calcium chloride was converted almost completely to the desired nitramine when introduced into acetic anhydride. Investigation showed that HCl from the $CaCl_2$ had been absorbed in the desiccator, and that this chloride had catalyzed nitramine formation. As proof of this, they repeated Bamberger's methods for the preparation of dimethylnitramine and nitropiperidine from the nitrate salt of the amine and acetic anhydride. The best yields obtainable were 22% and 6%, respectively. The same procedure, with the addition of five mol % zinc chloride, produced a 65% yield of dimethylnitramine and a 58% yield of nitropiperidine.

These investigators then undertook a study of the relative basicities of secondary aliphatic amines in acetic acid, by titration with sulfuric and perchloric acids (3). This study showed that those amines which could be nitrated directly without catalyst were more weakly proton-accepting than those which required the newly discovered chloride catalysis for successful direct nitration. This was in agreement with the earlier observation of the ease of nitration of negatively substituted secondary amines. For example, their titrations showed that imino-bis-acetic acid, $HOOC-CH_2-NH-CH_2-COOH$, is a weaker proton-acceptor than is di-n-butyl amine. The former is readily nitrated without catalyst, while the latter cannot be nitrated in the absence of chlorides.

An extensive study of the ease of nitration of secondary amines showed no exceptions to the above conclusions, and showed further that the amount of catalyst required increases as does the basicity of the amine (4). Thus the strongest amine investigated, diisopropylamine, requires a full equivalent of chloride to obtain satisfactory yields.

Finally, a thorough investigation of anomolous products in the nitration of lysidine, I, led to the theory that the active catalyst is electropositive chlorine formed by a variation of the aqua regia reaction (5). From the basicity of lysidine (3) it was expected that it could be nitrated to nitrolysidine, II, by using a few mol % catalyst. This procedure led only to dinitroimidazolidone, V. Attempted nitration using a full equivalent of catalyst yielded a new product, believed to be VII. This structure for the new compound is supported by its conversion to VIII, but not as yet by an alternate synthesis.

Formation of VII was explained by postulating addition of chlorine acetate to the olefinic bond in the ephemeral intermediate IV, an addition not without precedent. Thus electropositive chlorine, found to be present by analysis, was removed, accounting for the need to use a full equivalent of catalyst.



If electropositive chlorine is the active catalyst, it is possible that chloramines are intermediates in the nitrations considered.

It was found that the catalyst could be introduced in the form of HCl, $ZnCl_2$, acetyl chloride, or the hydrochloride of the amine being nitrated.

The following equations serve to illustrate possible steps in

the formation and stabilization of electropositive chlorine in the nitration mixture:

$$HNO_3 + HCl \rightleftarrows HOCl + HNO_2$$

$$HOCl + Ac_2O \rightarrow ClOAc + HOAc$$

One additional observation strengthening the postulates presented here is that the amount of nitrosamine formed by side reaction is dependent on the amount of catalyst used, as would be the amount of nitrous acid which might effect nitrosation.

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Reported by Bruce Englund
May 7, 1948

"F" AND "B" STRAIN IN ORGANIC COMPOUNDS

Introduction.--H. C. Brown, in the course of his studies on acids and bases in gaseous phase, explains the anomalous base strengths of methylamines by steric factors. Current theories of English school (1), in explaining the effect of a given substituent, stress the effect of that substituent upon the charge distribution within the molecule, more than the role played by the steric requirements of the substituents in altering the properties of the molecules.

If only polar factors of the alkyl groups were considered it would be predicted that the strength of the aliphatic amines should increase regularly with the number of alkyl groups (2).

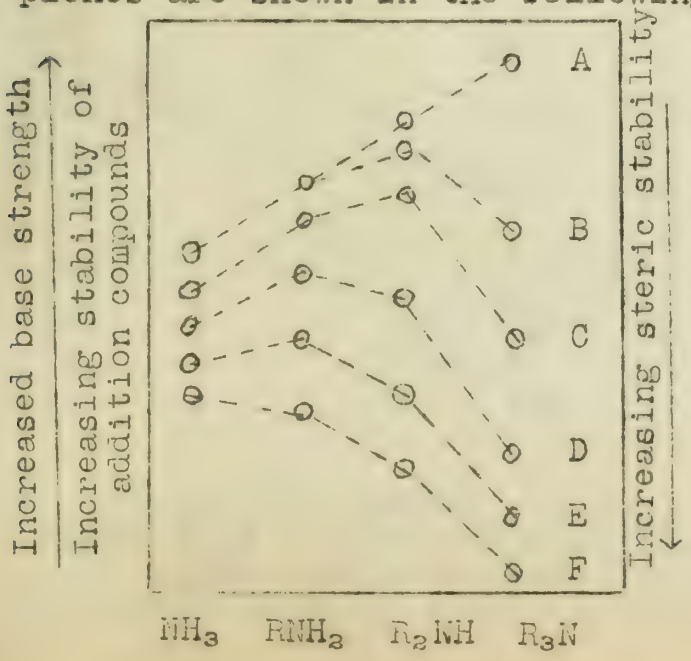
$$NH_3 < RNH_2 < R_2NH < R_3N$$

However, the order actually observed is

$$NH_3 < R_3N < RNH_2 < R_2NH$$

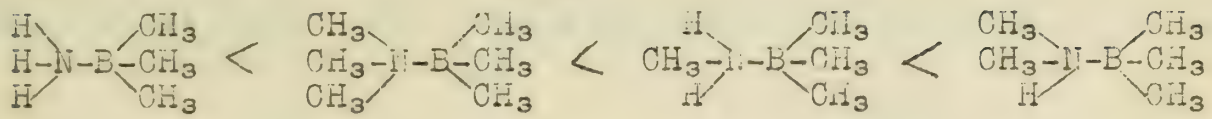
F-strain is caused by steric interference of atoms or groups which are attached to the acid and the base, resulting in a force which tends to separate the two (3). This strain derives its name from the fact that it is at the "interface" between two components and is "frontal". In many respects it is similar to steric hindrance.

Evidence for F-strain.--The relative strengths of the bases of ammonia, trimethyl-, triethyl-, tri-isopropyl-, and tri-t-butylamines was determined by using tri-methyl-, triethyl-, tri-isopropyl-, and tri-t-butylboron, as reference acids. A few of these results obtained by studies of dissociation constants of the complexes are shown in the following figure.

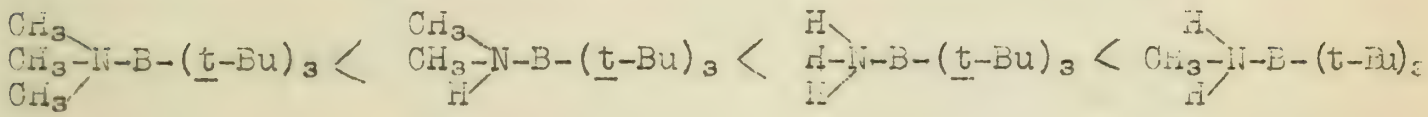


Amine Series	Reference Acid		
	H^+	$(CH_3)_3B$	$(t\text{-}C_4H_9)_3B$
Methyl.....	B	B	E
Ethyl.....	B	D	F
Isopropyl..	B	E	
t-Butyl....		F	

This relative order of base strengths



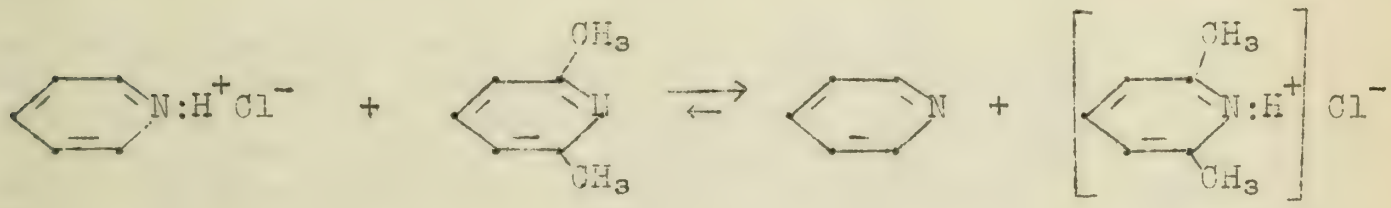
is observed with trimethylboron and is altered to



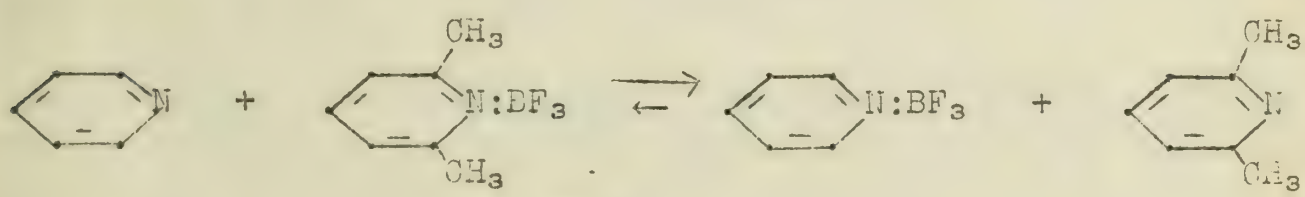
with tri-t-butylboron.

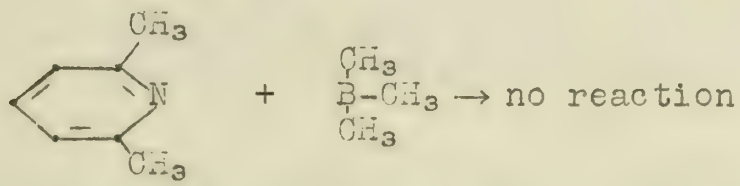
This change is in accord with the predicted effect of increased F-strain on the relative base strengths of ammonia and the methylamines (4).

Another example of the effect of F-strain is the behavior of pyridine and α,α'-lutidine (9). The latter is a stronger base than the former as shown by a competitive reaction with HCl.



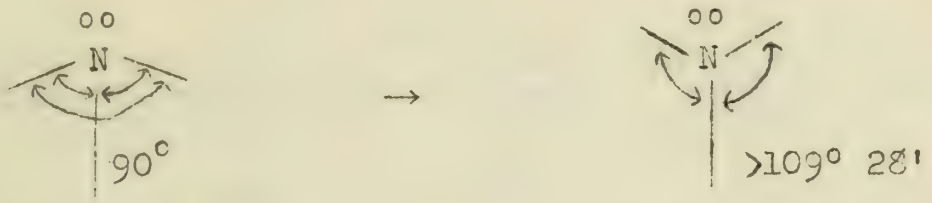
But pyridine displaces α,α'-lutidine from α-α'-lutidine-boron fluoride and trimethylboron does not even add to this base.





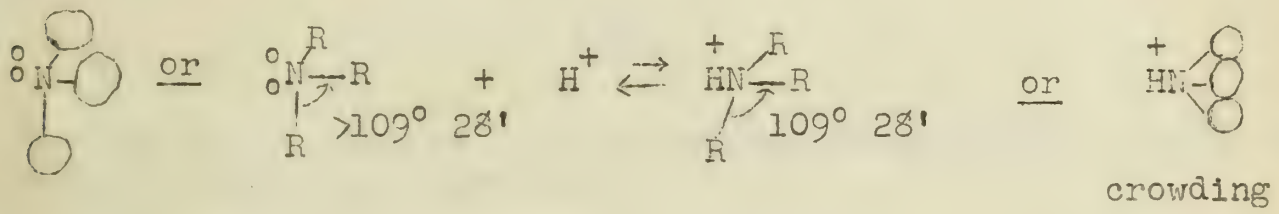
B-strain, however, is that strain which is introduced into a molecule as a result of changes brought about by the steric requirements of bulky groups attached to that atom (3). It was suggested that, in tertiary amines, the steric requirements of

three alkyl groups crowded about the small nitrogen atom are met by a spreading of the C-N-C bond angle from the 90° value predicted by quantum theory to a value somewhat greater than that of the tetrahedral angle (109° 28'). Such expansion of the bond angle is



Normal — Satisfying steric requirements

facilitated by the absence of a fourth group on the N atom. Addition of a proton (or other group) to the free electron pair tends



to reduce the expanded angle to the tetrahedral value. This results in increased crowding of the three alkyl groups and the introduction of considerable strain into the molecule. This strain (called B-strain since it is localized at the "back" of the amine molecule) causes the amine to resist the addition of proton (or other group) and leads to an apparent weakening of the strength of the base.

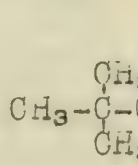
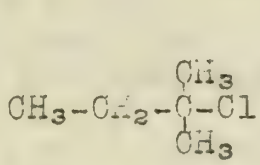
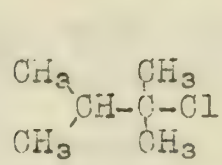
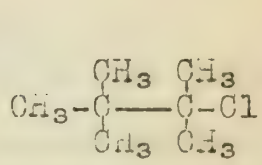
Considering the close similarity in the dimensions of N and C atoms, it follows that three alkyl groups about a C atom should also bring about a condition of strain.

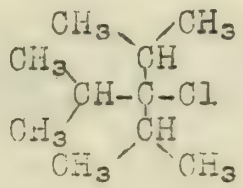
Evidence for B-strain in C Atoms.--(1) Molecular rearrangements. Alcohols with structure R_2CHCH_2OH and R_3CCH_2OH exhibit a marked tendency to undergo rearrangement in reactions involving removal or replacement of the hydroxyl group (5). In such rearrangements an alkyl group on the tertiary or quaternary C atom migrates. The marked lability of such groups is easily explicable in terms of strain postulated by B-strain hypothesis at such C atoms.

(2) Hydrolysis of alkyl halides. Ingold, Hughes and their coworkers have demonstrated that in the hydrolysis of tertiary halides ionization is the rate determining step, and have attributed this tendency to the cumulative inductive effect of three alkyl groups. Brown suggests that β-strain also facilitates hydrolysis (2). Such a strain should be relieved by the expansion of the bond angles to 120° in the presumably planar carbonium ion.

$$R_3CCl \rightarrow R_3C^+ + Cl^-$$

Bartlett (6) has given the relative rates of ionization of tertiary chlorides as follows:

relative rates in 1:3 acetone-water				
	1.00	2.06	1.75	2.43



6.91

The effect of size of alkyl groups in these can only be explained by B-strain hypothesis.

(3) Selective dehydration of alcohols.

$$R_2CHCHOHCH_2R \xrightarrow{\text{Dehydrate}} R_2C{=}CHCH_2R$$

Adjacent tertiary hydrogen, rather than secondary, is invariably lost. This has also been explained by Hyperconjugation Effect (7).

Some more work by Brown and coworkers has shown that the presence of two very bulky groups attached to a single atom may be the center of marked B-strain. The instability of di-t-butylether and di-t-butylamine is ascribed to this cause. A quantitative estimate of the B-strain in such compounds has been found to be of the order of 5 to 7 kcal, which can easily account for the observed behavior.

Recently doubts have been raised by Spitzer and Pitzer (8) regarding the B-strain hypothesis. They have made a semi-quantitative calculation of the magnitude of the B-strain by considering the energy increment due to the change in the C-N-C bond angle when trimethylamine is added to trimethylboron. This they have found to be 0.5 kcals, a value far too small to account for the observed anomaly.

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Reported by A. S. Nagarkatti
May 14, 1948

x AND y BANDS IN ABSORPTION SPECTRA

Lewis and Calvin (1) have presented a simplified picture of the mechanism involved during absorption of light by organic molecules. The unsaturation, or π electrons of a molecule containing conjugated unsaturated bonds are considered to function as a unit upon interaction with light, and the frequency of the light which a molecule can absorb is determined by the force needed to displace this cloud of π electrons. The greater the force, the higher the frequency. This force, equal and opposite to the so-called restoring force of the electron cloud, decreases with lengthening of the conjugated system and also upon introduction into the system of electron releasing groups, such as amino or hydroxyl groups.

It was suggested by Lewis and Calvin that when a molecule having a conjugated system extending in two dimensions interacts with light the oscillation of the electron cloud should be resolvable into two orthogonal oscillations, one in the direction of minimum restoring force, and the other in the direction of maximum restoring force. These two oscillations should manifest themselves as two bands in the absorption spectrum. The direction of minimum restoring force or maximum polarizability in the molecule is conventionally taken as the x direction, and the corresponding spectral absorption region is called an x band. Similarly, the direction of maximum restoring force or minimum polarizability is designated as the y direction and the corresponding spectral band called a y band. Thus the y band would always appear at shorter wave lengths than the x band.

This x and y band theory was not pure conjecture but was based on existing evidence. It was known from studies of crystals that the position of a molecule relative to the electric vector of polarized light is important in determining the extent of light absorption. Moreover, the behavior of certain fluorescent dyes when exposed to polarized light could be readily explained on the basis of the theory.

When a solution of sodium fluorescein is exposed to vertically polarized light of wave length corresponding to the main, long wave length absorption band of the dye, the resulting fluorescence is also polarized vertically. If, on the other hand, the exciting light has a wave length lying within the weaker, shorter wave length absorption band, the fluorescence is polarized horizontally. If it is assumed that the two absorption bands are x and y bands in the sense implied by the Lewis and Calvin theory, then the above phenomenon may be explained as follows.

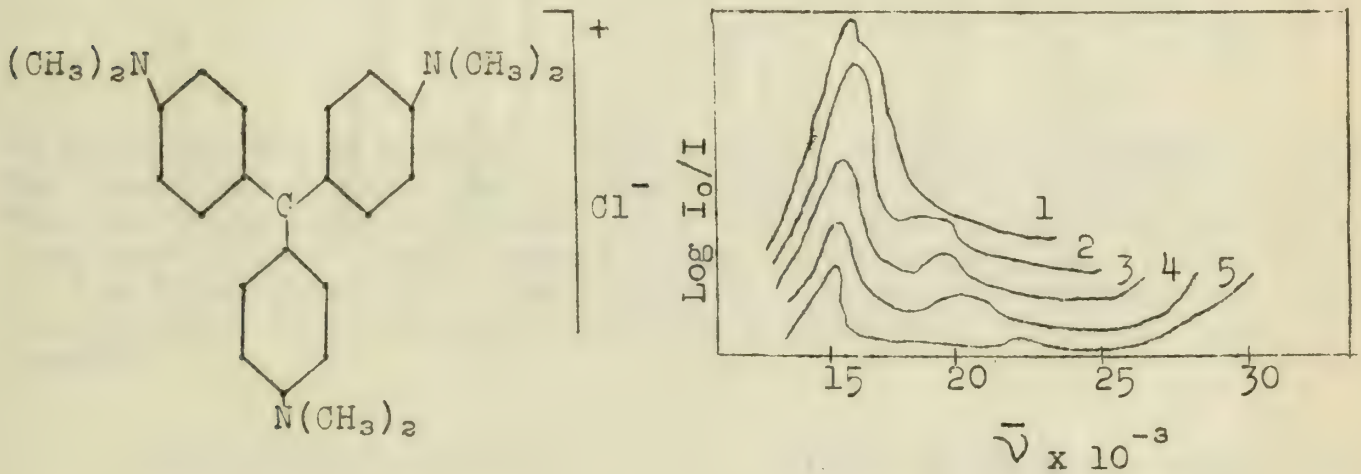
When the dye solution is irradiated within the x band those molecules with their axes of maximum polarizability parallel to the electric vector of the exciting light are activated in preference to molecules oriented otherwise, while molecules with their axes of maximum polarizability perpendicular to the electric vector remain undisturbed. Assuming that the molecules do not change position during excitation and fluorescence, the displaced electron cloud, characteristic of the excited state, returns to its equili-

brium position generating fluorescent light polarized in the same direction as was the exciting light.

When the exciting light has a wave length corresponding to the y band the molecules with their axes of minimum polarizability parallel to the electric vector of the light are activated preferentially. These activated molecules do not immediately lose all of their energy as fluorescence but fall first to that same lower energy state which results when the molecules are irradiated in the x band. Now when the electron cloud returns to its equilibrium position it travels in a direction perpendicular to the electric vector of the exciting light, and the resulting fluorescence is consequently polarized at right angles to the direction in which the exciting light was polarized.

Once the x and y band theory had been expounded, experiments were devised for the purpose of determining if there actually does exist a correspondence between certain spectral bands and direction of electronic motion within molecules.

The molecule of crystal violet,

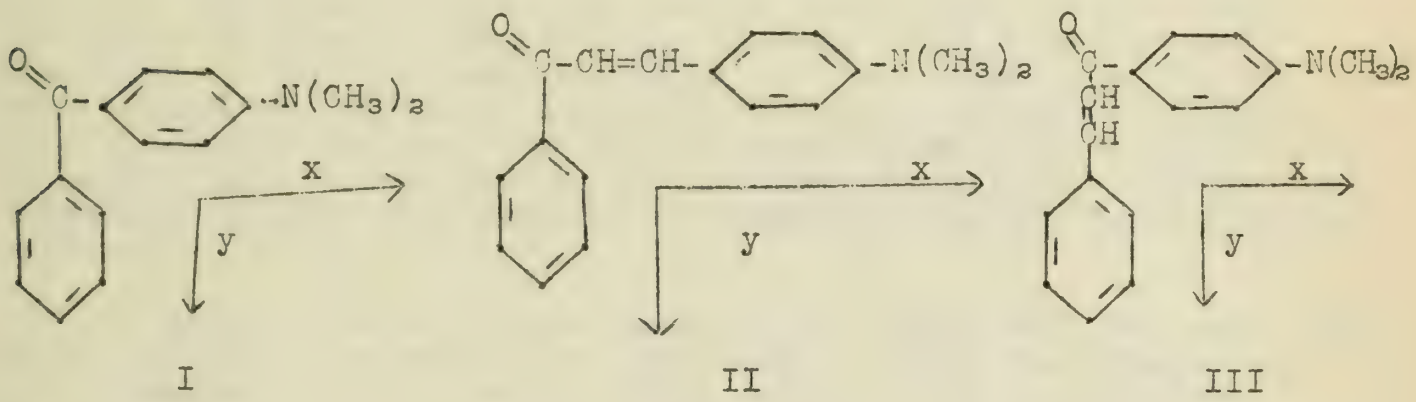


1. Crystal violet with a pair of methyls replaced by a pair of ethyls.
2. p-Methoxy malachite green.
3. p-Methyl malachite green.
4. Malachite green
5. The ion of Michler's hydrol.

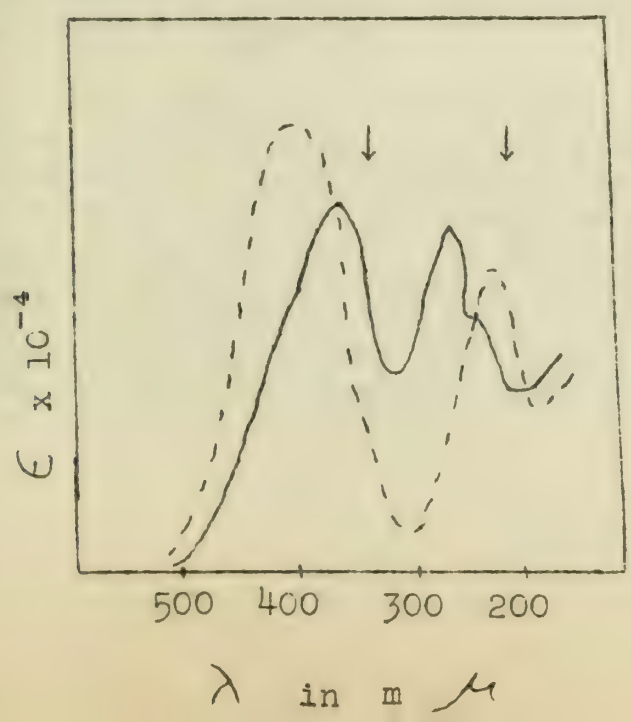
has a center of symmetry, and therefore the polarizability is the same in the x and y directions. The absorption spectrum is characterized by one broad band. If the theory of x and y bands is correct, destroying the center of symmetry should cause the absorption band to split into two bands. That such splitting actually occurs was demonstrated beautifully by Lewis and Bigeleisen (2). The degree of splitting was found to vary directly with the extent of departure from symmetry, just as was anticipated. More-

over, this evidence was correlated nicely with the fluorescence phenomenon described above by showing that irradiation within the new, higher frequency band which results on removal of symmetry produces fluorescence polarized at right angles to the direction of polarization of the exciting light.

Katzenellenbogen and Branch (3) used a different line of attack. Starting with an already asymmetric molecule, p-dimethylaminobenzophenone, they altered the polarizability of the molecule in either the x or y direction by introducing a vinyl group on either one or the other side of the carbonyl.



In good agreement with the theory under scrutiny, introduction of the vinyl group into the conjugated system lying along the axis of maximum polarizability moved only the longer of the two principal long wave length bands toward longer wave length, while introduction of the vinyl group into the conjugated system of minimum polarizability moved only the shorter wave length band to longer wave length.



—— III (p'-dimethylaminochalcone)

- - - - II (p-dimethylaminochalcone)

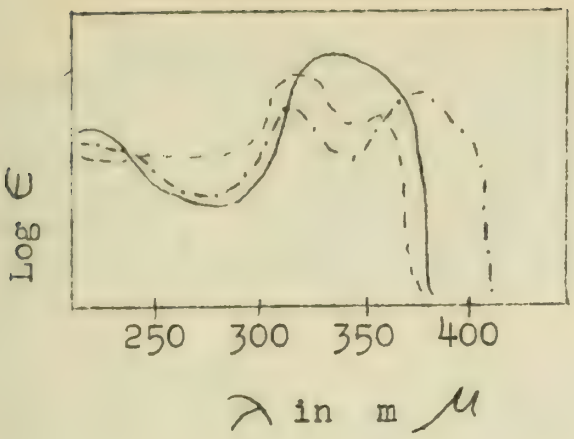
Arrows indicate positions of x and y bands for I.

(p-dimethylaminobenzophenone)

The so-called cis-bands which appear in the spectra of some carotenoids can be explained on the basis of the theory under consideration (4). When an all trans carotenoid is isomerized to a partly cis compound, a new absorption band appears in the spectrum on the high frequency side of the main absorption band. This new absorption region is called a cis-band. Light absorption by an all trans carotenoid involves an oscillation of the electron cloud in the x direction, there being practically no extension of the molecule in the y direction. When one cis linkage is placed in the center of the conjugated chain, however, there results a considerable extension in the y direction, so that on the basis of the x y band theory one would expect to find a new absorption band appearing at shorter wave length, corresponding to electronic oscillations in the y direction. The theory would also predict that introduction of more than one cis linkage would diminish the intensity of the cis-band, which we are now considering to be a y band, since the extension in the y direction is also diminished. This prediction is born out by the observation that the cis-band is absent in a carotenoid having practically all cis linkages but appears when such a carotenoid is isomerized to the partly trans compound.

R. Norman Jones (5) has employed the ideas of Lewis and Calvin to aid in bringing some order into the realm of the complex spectra of polynuclear hydrocarbons. Such molecules have conjugated systems extending in two dimensions, and so it should be possible to distinguish x and y bands in their spectra. Jones was able to identify such bands by noting that either one or the other of two broad regions of the absorption spectrum of a polynuclear hydrocarbon was affected by introducing electron releasing groups into the molecule. When such a group was located so as to increase the maximum polarizability of the molecule, only the long wave length region of the spectrum was affected, while placing the group in a position where it could increase the minimum polarizability of the molecule affected the short wave length region. In either case the absorption region affected was shifted to longer wave lengths, as would be expected.

The absorption spectra of certain aldazines have been elucidated with the help of x and y band theory (6). p,p'-Dihydroxybenzalazine, $(p\text{-}HOC_6H_4CH{=}N)_2$, has one broad adsorption band presumably due to electronic oscillations along the major, or x axis of the molecule. If the hydroxyl groups are moved into the meta or ortho positions, a new absorption band appears. The hydroxyl groups in the meta and ortho positions increase the polarizability of the molecule in the y direction, and it is assumed that the new spectral band is due to electronic oscillations in this direction.



—— p,p'-dihydroxybenzalazine

- - - - m,m'-dihydroxybenzalazine

-·-·-·- o,o'-dihydroxybenzalazine

This seminar has been concerned with x and y bands only, however, it should be mentioned for the sake of completeness that certain spectral bands have been identified with electronic oscillations perpendicular to the plane of a molecule (1) and with the first harmonic of electronic oscillations in the x direction (7). These bands are designated as z bands and x' bands respectively.

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Reported by Paul M. Mader
May 14, 1948

ALIPHATIC FLUORINE COMPOUNDS

Introduction.--The majority of aliphatic fluorine compounds already recognized are prepared by the action of metallic fluorides on the corresponding iodides, bromides, and chlorides. The most commonly used metallic fluorides are AgF (1), ZnF_2 (2), HgF_2 (3), TlF (4), CoF_3 (5), and SbF_3 (6) (the last in the presence of bromine). Of these, CoF_3 and SbF_3 are the most useful. Antimony trifluoride is used in the industrial preparation of "Freon" (7).

$$CCl_4 \xrightarrow[HF]{SbF_3} CCl_2F_2$$

In general, however, it is difficult to introduce fluorine into a molecule containing oxygen by the use of metallic fluorides. Other methods, for example, direct fluorination (8) and the addition of HF to a double bond (9), have been tried repeatedly, but they usually yielded mixtures which were difficult to separate.

Use of KF.--A very reactive halogen, such as that of an acyl or sulfonyl halide, is readily replaced by fluorine by the action of potassium fluoride (10). Until recently, however, all attempts to replace less active halogens with fluorine using this reagent have resulted in very low yields of the desired fluorinated product. Henne (11) has attributed these low yields to the slowing and eventual stopping of the reaction because of the formation of a coating of potassium halide over the reagent.

Gryszkiewicz-Trochimowski, during World War II, was able to overcome these difficulties (12). He succeeded in adapting the use of potassium fluoride to the preparation of fluorine-substituted esters (12), alcohols (13), and acids (12), obtaining excellent yields. The conditions required are the following:

1. Complete absence of water.
2. KF in excess, in a powdered form.
3. Temperatures in the range 150-250°C.
4. Mechanical agitation.

The reaction is carried out in an autoclave.

The use of a 10 to 50% excess of KF is advisable, especially when the product exhibits a tendency to lose HF during the reaction. This excess prevents the liberation of HF, thus simplifying the purification procedure and permitting the use of glass reaction vessels.

It is interesting to note that NaF will not cause the replacement of chlorine by fluorine (14).

Fluorine-Substituted Esters (12).--The esters of fluoroacids

may be prepared in good yield by the exchange of chlorine, bromine, or iodine for fluorine, using KF as the fluorinating agent. For example, methyl fluoroacetate has been prepared in 90% yield from methyl chloroacetate.

$$ClCH_2CO_2CH_3 \xrightarrow{KF} FCH_2CO_2CH_3$$

The ethyl and methyl esters of fluoroacetic, fluoroformic, α-fluoropropionic, and fluoromalonic acids have been prepared from the corresponding chloro-compounds in yields ranging from 60 to 90%.

The esters of fluoroalcohols may be prepared in the same manner. For example, 2-fluoroethyl acetate has been prepared in 50% yield from 2-chloroethyl acetate.

$$CH_3CO_2CH_2CH_2Cl \xrightarrow{KF} CH_3CO_2CH_2CH_2F$$

The acetates of ethylene fluorohydrin, trimethylene fluorohydrin, and tetramethylene fluorohydrin have been prepared from the corresponding chloro-compounds.

The esters which are not stable at higher temperatures are prepared in rather low yields because of their tendency to lose HF and form the corresponding unsaturated compound. For example, the ester of α-chloropropionic acid yields a considerable quantity of acrylic ester when treated with KF.

$$CH_3CHClCO_2R \xrightarrow{KF} CH_3CHFCO_2R \xrightarrow{-HF} CH_2{=}CHCO_2R$$

<u>Fluorine-Substituted Alcohols and Acids (12,13)</u>.--It is not feasible to prepare fluoroacids and fluoroalcohols by the direct reaction of the corresponding chloro-compounds with KF. However, the ester of the desired compound is readily obtained, and yields the fluoroacid or alcohol upon saponification.

In this manner the following compounds have been prepared: γ-fluoropropanol, β-fluoroethanol, β-fluoroisopropanol, and δ-fluoro-<u>n</u>-butanol. The yields range from 75 to 80%.

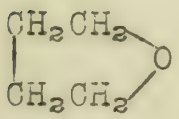
<u>β-fluoropropionic and γ-fluorobutyric Acids (14)</u>.--The direct synthesis of β-fluoropropionic and γ-fluorobutyric acids by replacement of chlorine by fluorine is not possible because of the instability of the chloroesters at the reaction temperature. However, by modification of the procedure, these acids may be obtained in satisfactory yields.

The synthesis of β-fluoropropionic acid has been effected in the following manner:

$$HOCH_2CH_2CH_2OH \xrightarrow{S_2Cl_2} HOCH_2CH_2CH_2Cl \xrightarrow{Ac_2O} CH_3CO_2CH_2CH_2CH_2Cl$$

$$\xrightarrow{KF} CH_3CO_2CH_2CH_2CH_2F \xrightarrow{H_2O} HOCH_2CH_2CH_2F \xrightarrow{[O]} HO_2CCH_2CH_2F$$

γ-Fluorobutyric acid has been obtained as follows:



$$\xrightarrow{CH_3COCl} CH_3CO_2CH_2CH_2CH_2CH_2Cl \xrightarrow{KF} CH_3CO_2CH_2CH_2CH_2CH_2F$$

$$\xrightarrow{H_2O} HOCH_2CH_2CH_2CH_2F \xrightarrow{[O]} HO_2CCH_2CH_2CH_2F$$

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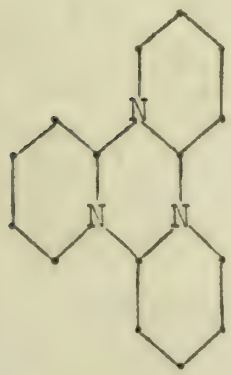
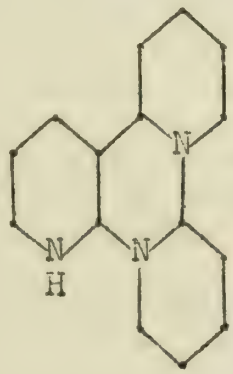
Reported by William Goode
May 14, 1948

THE POLYMERIZATION OF Δ^1 PIPERIDEINE

Of the three known trimers of Δ^1 piperideine (I) two have been previously described and erroneously characterized in the literature. Schöpf and coworkers (1) recently have carried out an extensive investigation of the structure and reactions of these two compounds (II and III) and have isolated a hitherto unknown stereoisomer of one of them.



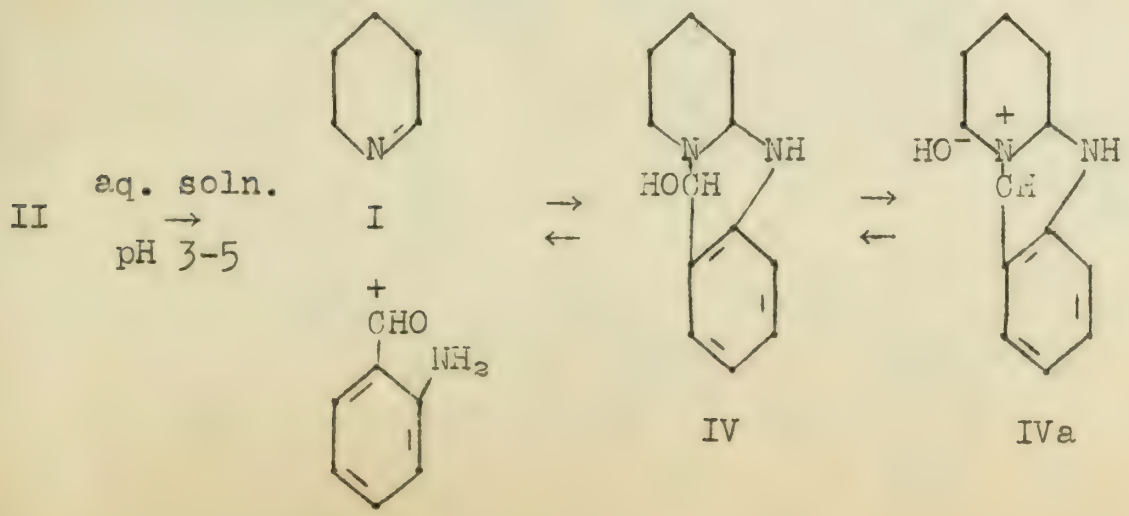
II



III

I

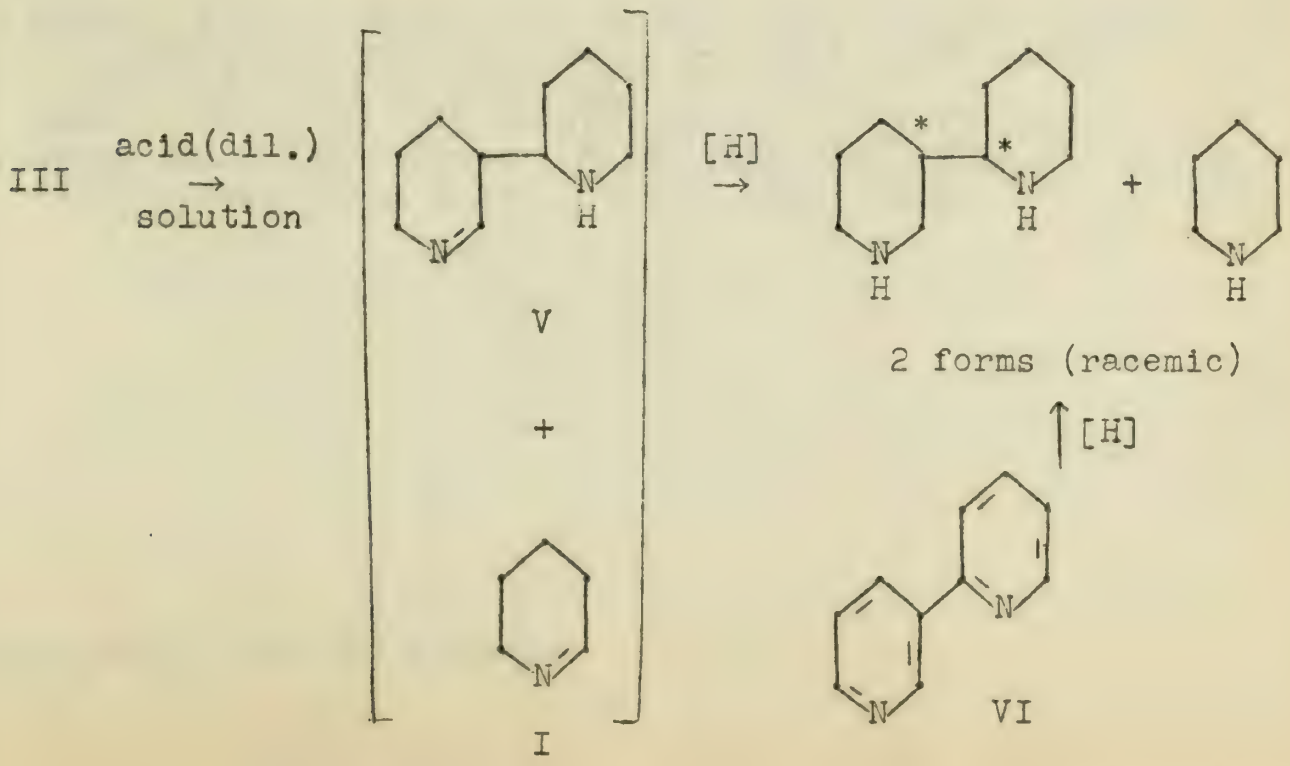
Compound II, α-tripiperideine, was obtained by the reaction of calcium hypochlorite with piperidine to give N-chloropiperidine and subsequent treatment of this with boiling alcoholic potassium hydroxide to yield Δ^1 piperideine (1,2). The latter, on cooling of the alkaline solution, polymerized to α-tripiperideine. Lellmann and Schwaderer (2) believed the compound was a dimer but Schöpf has presented considerable evidence in support of structure II. The analysis and molecular weight in benzene indicate the empirical formula $(C_5H_9N)_3$. Methane is not evolved when the compound is treated with methyl magnesium iodide at room temperature. In the catalytic hydrogenation of II in dilute acid solution, three moles of hydrogen are consumed to give a quantitative yield of piperidine. Finally α-tripiperideine reacts with ortho aminobenzaldehyde at 25° as shown in the following scheme:



This reaction is exactly analogous to the thoroughly investigated reaction of Δ^1 pyrroline with ortho aminobenzaldehyde (3). The picrate of IVa is obtained in quantitative yield and its structure is proved by oxidation with chromic oxide to the known 2,3-tetra methylene quinazolone-4. These observations place the double bond definitely in the 1,2 position of compound I and show that α-tripiperideine, in dilute acid solution, dissociates easily to the monomer.

Structure II contains three similar asymmetric carbon atoms and, therefore, it should exist in two racemic modifications. A second form, β-tripiperideine, was obtained by Schöpf in several preparations as the main product instead of α-tripiperideine. Its chemical behavior is identical with that of α-tripiperideine. It is easily converted to the more stable α-isomer, and its formation is probably favored by allowing the polymerization of Δ^1 piperideine to take place at low temperatures.

Compound III, isotripiperideine, was isolated in two instances (4,5) previous to Schöpf's work. Ahrens identified it as a dimer and Ivastchenko and Kirsanov, checking his work, found it to be a trimer but assigned to it the structure II. Schöpf obtained it by the alkaline hydrolysis of α-amino-N,N'-diacetylpiperidine, by the isomerization of α-tripiperideine in refluxing acetone with piperidine hydrochloride as catalyst, and as a component of the N-chloropiperidine-alcoholic potassium hydroxide reaction mixture. While isotripiperideine is shown to have the formula $(C_5H_9N_3)_3$ it reacts, under the same conditions, quite differently from α-tripiperideine. One mole of methane (per mole) is evolved when the compound is treated with the methyl Grignard reagent. Hydrogenation of isotripiperideine yields, besides piperidine, equal quantities of the two possible racemic α,β'-dipiperidyls. Hydrogenation of α,β'-dipyridyl (VI) yields the same two racemic compounds.



The treatment of isotripiperideine with ortho aminobenzaldehyde and subsequently with picric acid yields two picrates - one identical with that of IVa and the other a dipicrate of the pseudo base (corresponding to IVa) resulting from the condensation of V, tetrahydroanabasine, with ortho aminobenzaldehyde. Thus two piperideine residues in isotripiperideine must be joined through a C-C bond from one α position to the other β position.

In accordance with the proposed structures for α- and isotripiperideine, α-tripiperideine is found to be the less stable of the two since it is more easily hydrogenated and it is readily converted into isotripiperideine.

Other reactions of II and III indicate structural differences between the two substances. α-Tripiperideine reacts with phenylisothiocyanate to yield a product containing two molecules of Δ^1 piperideine and one of the reagent whereas isotripiperideine gives a product containing two molecules of Δ^1 piperideine (or one of tetrahydroanabasine, V) and two molecules of the reagent. Similarly a monoacetyl derivative is obtained from α-tripiperideine but a dimolecular diacetyl derivative in addition to the monoacetyl compound is obtained from isotripiperideine. One noteworthy exception to these differences in behavior of the two compounds is the reaction of both II and III with ortho aminobenzaldehyde at 100° to yield β(ω-aminopropyl)quinoline.

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Reported by Janet B. Peterson
May 14, 1948

SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF PHENANTHRIDINE COMPOUNDS

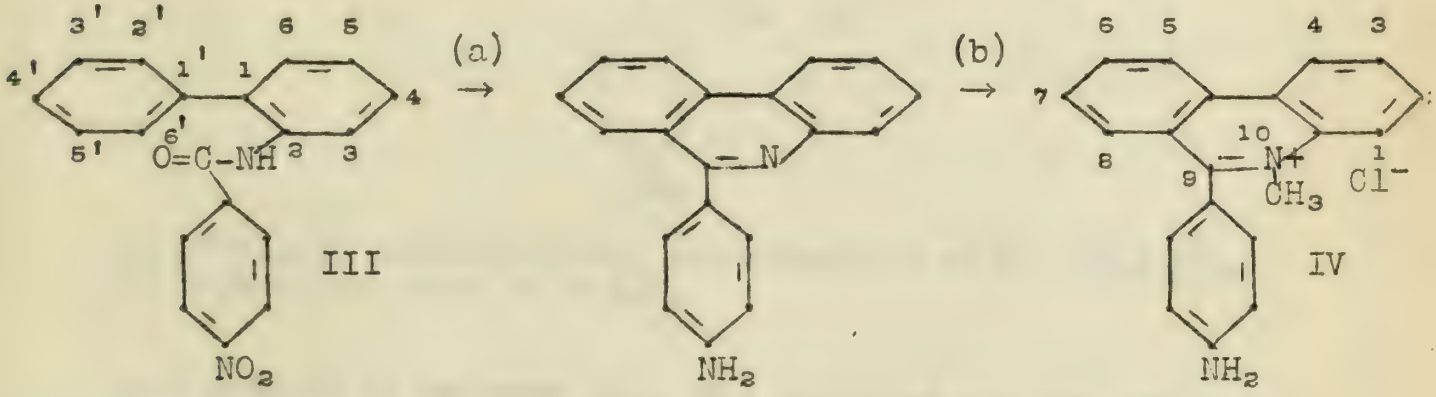
A systematic study of phenanthridine compounds was begun by Morgan and Walls (1) in 1931 to determine their applicability as chemotherapeutic agents. It was thought that they would be of interest in chemotherapy for several reasons: (a) Phenanthridine (I) contains a quinoline ring system, which is present in quinine and several synthetic antimalarials. (b) It contains an isoquinoline ring system which is present in many physiologically active alkaloids. (c) It is isomeric with and analagous to acridine (II), the parent substance of the antimalarial atebrin and many antiseptics.

I

II

Most of the early work on phenanthridines was done between 1889 and 1905 by Pictet and coworkers (2,3,4).

The following method of synthesis was devised by Morgan and Walls and was used to prepare several compounds (1,5,6).



(a) Cyclization with $POCl_3$. Reduction with Fe + H_2O.
(b) Acetylation, quaternation, deacetylation.

It was found (7) that the presence of an amino group and the quaternary function in the phenanthridine molecule or in 9-phenyl phenanthridine (see IV) conferred moderate antiseptic properties which had the important and unusual merit, also shown by the amino acridine series, of being quite stable and often enhanced in serum.

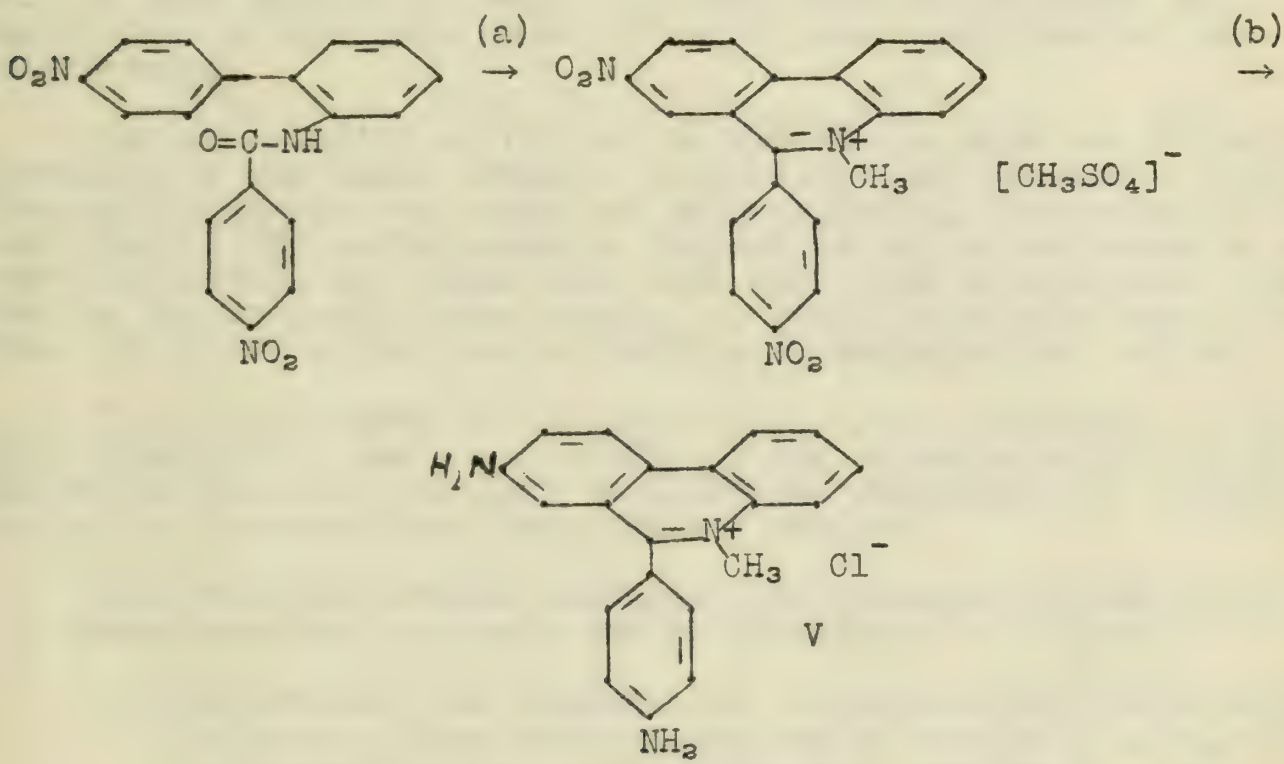
To obtain a closer analogy to the acriflavine molecule the preparation of compounds with two amino groups was carried out. Low yields were obtained with the above method with compounds containing a nitro group in the 4' position because of difficulty of ring closure.

II

I

A valuable improvement in the method was the introduction of an inert, high-boiling solvent such as nitrobenzene, which resulted in an increase both in the rate of condensation and in the yield of product (7). The favorable influence of the nitrobenzene is believed to be not entirely a thermal effect, but is also associated with its known properties as an ionizing solvent. In several cases the yield of phenanthridine derivatives was increased from a small amount to over 50%.

Another improvement in the method was the direct quaternation of the nitro compound:

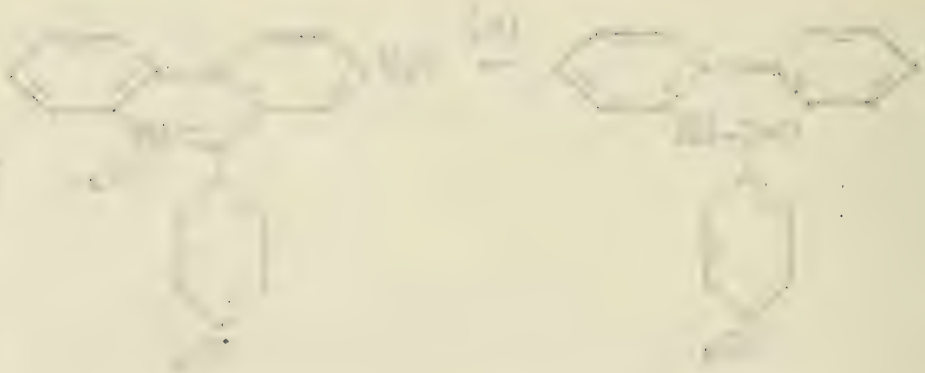


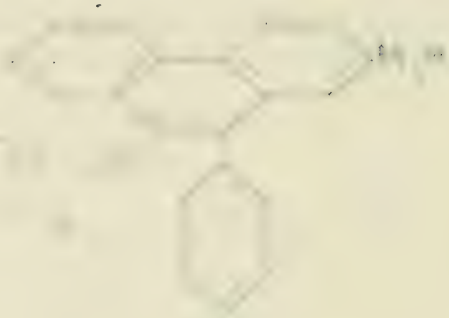
(a) $POCl_3$ in nitrobenzene, quaternation with $(CH_3)_2SO_4$.
(b) Reduction with Fe + H_2O.

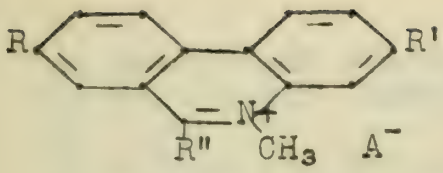
This method is shorter than the previous one by two steps: Acetylation and subsequent deacetylation.

The quaternary salts with two amino groups (such as V) were found to possess marked activity against the organism responsible for bovine trypanosomiasis, a disease related to human sleeping sickness (8). This organism is resistant to the most active of previously known trypanocides and no really adequate drug treatment had been available.

A considerable number of mono- and di-amino phenanthridine derivatives were prepared, the most active being the following:







V: R = NH_2, R' = H, R" = p-$C_6H_4NH_2$, A = Cl.
VI: R = NH_2, R' = H, R" = m-$C_6H_4NH_2$, A = Cl.
VII: R = R' = NH_2, R" = C_6H_5, A = Br.

Compound V was prepared on a plant scale and was given a full trial with infected cattle under field conditions. It was found to be quite effective but had several disadvantages: (a) the margin between curative and toxic doses was too small, (b) the solubility was too low, and (c) it required intravenous injections. Compound VII is more soluble in water and has a much wider range of activity. It has been found effective when administered subcutaneously.

The superiority of VII may be associated with the "benzidine" position of the amino groups. In salts of the benzidine type, a benzenoid-quinoid resonance may be postulated. According to Kumler and Daniels (9) bacteriostatic properties in the sulfonamide and acridine series are associated with this type of resonance, but so far in the phenanthridine series, no clear conclusion can be drawn that it favors either bacteriostatic or trypanocidal action.

The significance of the quaternary cyclic nitrogen has been determined (10): the quaternation of the nitrogen of a typical quinoline antimalarial such as pamaquine destroyed the antimalarial activity, but developed trypanocidal action.

The relation between structure and pharmacological activity of phenanthridine compounds may be summarized as follows:

(a) In general, the presence of a quaternary nitrogen atom leads to a distinct enhancement of action in serum (6). No paraciticidal activity has been observed in any phenanthridine compound not possessing a quaternary function.
(b) An amino group in the 7 position confers trypanocidal activity which is increased to a maximum when a second amino group is present.
(c) All the di-amino derivatives exhibit trypanocidal activity except those in which the amino substituents are restricted to the 9-phenyl group.
(d) The greatest activity is observed in those compounds possessing a benzidine type structure, although many compounds without such a structure possess considerable activity.

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Reported by Anton Mudrak
May 21, 1948

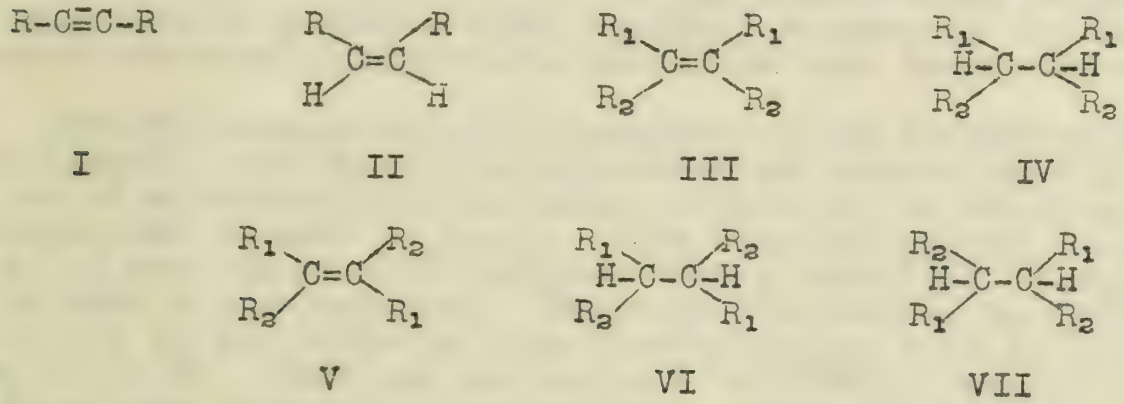
SELECTIVE CATALYTIC HYDROGENATIONS

Selective catalytic hydrogenation is the term applied to the preferential reduction by hydrogen in the presence of catalysts under various experimental conditions of: (1) a single functional group in a polyfunctional molecule, such as unsaturated carbonyl compounds, (2) cis-trans isomers, and (3) a component of a mixture.

This selectivity may be accomplished by (1) changing the temperature, (2) by using promoters, (3) by changing the catalyst, and (4) by changing the amount of catalyst.

I. Cis-Trans Isomers.

Change in Temperature.--If catalytic hydrogenation is regarded as the simultaneous addition of two atoms of the same hydrogen molecule, it follows that the hydrogen atoms will always be added to a double bond or triple bond in cis-position. Farkas (9) has formulated the following rules concerning the formation of stereochemical isomers in the hydrogenation of unsaturated hydrocarbons. They do not apply to unsaturated alcohols and acids.



1. Acetylene derivatives of the type (I) will give cis-ethylene compounds of the type (II).
2. Cis-ethylene compounds of the type (III) will give meso compounds of the type (IV).
3. Trans-ethylene compounds of the type (V) will give a racemic mixture of the optically active forms (VI) and (VII).

In hydrogenations with nascent hydrogen, or at higher temperatures, the stable trans isomers will be formed in each case, since then the hydrogenation involves the consecutive addition of two independent hydrogen atoms. The resulting compounds are usually the trans compounds if acetylene derivatives are hydrogenated and meso compounds if ethylene derivatives are hydrogenated. The following evidence is given in support of the above rules.

Tolane	catalytic →	cis-stilbene
Tolane	nascent hydrogen →	trans-stilbene
cis-Dimethylstilbene	catalytic →	meso form
trans- imethylstilbene	catalytic →	racemic forms

	Pt, 25°	Ni, 180°
o-Xylene	cis-1,2-Dimethylcyclohexane	trans
p-Xylene	cis-1,4-Dimethylcyclohexane	trans
naphthalene	cis-Decalin	trans-Decalin

Farkas states that under the conditions of high temperature the cis compounds are transformed into the stable trans compounds. An exception is m-xylene which yields a mixture of the cis and trans-1,3-dimethylcyclohexanes at low or high temperatures.

Ott (5) studied the hydrogenation of the sodium salts of dimethylfumaric and dimethylmaleic acids and showed that by proper choice of experimental conditions, either cis or trans addition of hydrogen may be made to occur. With dimethylfumaric acid, the ratio of meso to racemic products varies depending on whether Ni or Pd is used as the catalyst. There is practically no difference in the ratio of the products when dimethylmaleic acid is hydrogenated with Ni or Pd. When the sodium salt of dimethylfumaric is hydrogenated at room temperature with highly active Pd-charcoal, the amounts of the dimethylsuccinic acids produced are 61% of the meso form and 39% of the d-l mixture. In neutral solution, the velocity of addition is decreased and the ratio becomes 30% meso and 70% d-l. With Zn and HAc at 80° a ratio of meso to d-l of 58:42 can be obtained. With Ni and animal charcoal the velocity of addition is at a minimum and the d-l dimethylsuccinic acid can be made the only product.

Paal (6,7) showed that the cis forms of the following compounds are more rapidly reduced with Pd and hydrogen than the trans forms: maleic-fumaric, oleic-elaidic, crotonic-isocrotonic, cis- and trans-o-ethoxycinnamic acids, and stilbene-isostilbene. This conclusion that the cis isomer should always be hydrogenated faster, considering other conditions such as room temperature, alcoholic or aqueous solution, and Pd-catalyst unchanged, became known as the "Paal Rule". It was thought that a relatively simple method for determining geometric configurations should be derived from the "Paal Rule".

Linstead (8) showed that hydrogenations of diphenic acid with Adams' catalyst yield cis and syn perhydro diphenic acids.

Change in Amount of Catalyst.--Csürös (10) studied the velocity differences in the hydrogenation of cis and trans isomers by varying the amounts of colloidal-Pd catalyst. He showed that the velocity of the hydrogenation is not a linear function of the amount of catalyst used but changes by following a maximum-minimum curve. He showed that there are definite amounts of catalysts at which the cis isomers are hydrogenated more readily than the trans isomers. However, above and below this range, hydrogenation of the trans isomers proceeds more readily. This phenomenon was observed with the following cis-trans acids: maleic-fumaric, oleic-elaidic, crotonic-isocrotonic, angelic-tiglinic, erucic-brassidic, citraconic-mesaconic, and the cinnamic acids.

The selectivity obtained by varying the amount of catalyst proved to be valid for the following catalysts: colloidal Pd, Pd precipitated on $BaSO_4$, Pd and Pt precipitated on animal charcoal, and colloidal Pt (11).

II. Unsaturated Carbonyl Compounds.

Unsaturated aldehydes are completely reduced to the saturated alcohols unless special conditions are used. The carbonyl group of ketones is reduced more slowly than in the case of aldehydes. Unsaturated ketones are reduced first to the saturated ketones and then to the saturated secondary alcohols.

Use of Promoters.--Work by Adams (1) showed that an unsaturated aldehyde can be reduced to an unsaturated alcohol with platinum if a trace of ferrous salt is added to promote reduction of the carbonyl group and also a trace of zinc acetate to inhibit the reduction of the double bond. In this way, citral was reduced to geraniol, and cinnamaldehyde to cinnamyl alcohol (1,2).

The selective reduction of the double bond in an unsaturated aldehyde is difficult to accomplish directly. The saturated aldehydes can be made by first making the acetal, reducing, and then hydrolyzing the saturated acetal. This has proved to be the best method for converting furfural into tetrahydrofurfural (3).

Hydrogenations similar to those made by Adams (1) on unsaturated aldehydes were made by Csürös (4) on unsaturated ketones. He used colloidal-Pd as catalyst in alcoholic solutions in the presence of $FeSO_4$. He selectively reduced the carbonyl group in benzalacetophenone and benzalacetone to the corresponding unsaturated secondary alcohols.

Change in Amount of Catalyst.--A change in velocity arising from different amounts of catalyst was also observed in compounds containing an olefinic linkage and a carbonyl group. Csürös (12) succeeded in selectively hydrogenating unsaturated aldehydes with colloidal Pd. The hydrogenation of cinnamic aldehyde was interrupted after one mole of hydrogen had been taken up. It was found that by varying the amount of catalyst, in one case, the carbonyl group could be reduced more readily, yielding cinnamyl alcohol, while in another case, the double bond could be selectively hydrogenated, yielding beta-phenylpropionaldehyde.

In another series of experiments with a definite amount of colloidal-Pd catalyst, Csürös showed that the carbonyl group of aliphatic unsaturated aldehydes and ketones does not undergo hydrogenation. On the other hand, under the same conditions, aldehydes and ketones of an aromatic character may be readily reduced. Crotonaldehyde took up one mole of hydrogen in each case yielding butyraldehyde, while cinnamic aldehyde and benzalacetophenone took up two moles to give the corresponding saturated alcohols.

Sello (11) hydrogenated phenylacetaldehyde to beta-phenylethyl alcohol with colloidal Pd precipitated on animal charcoal. Aliphatic unsaturated ketones and aldehydes, e.g. crotonaldehyde, tiglic aldehyde, methylheptenone were reduced to the saturated carbonyl compounds, butyraldehyde, the saturated tiglic aldehyde, and the methylheptanone, but they could not be reduced further to the corresponding saturated alcohols even when promoters like $FeSO_4$ were used.

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Reported by Alex Kotch
May 21, 1948

FRACTIONATION OF HIGH POLYMERS

High polymers, natural and synthetic, are not pure compounds. They are mixtures of chains, built up of the same units but of varying molecular weight. They may include straight chains, branched chains, and cross-linked networks. The physical properties of the polymer, in general, vary considerably with the molecular weight or degree of polymerization. In order to study the relationship between physical properties and molecular weight, it becomes desirable to separate the various molecular weight fractions and evaluate the properties of each. It is desirable to know this distribution also from the viewpoint of controlling synthetic reactions. Fractionation also is essential in research on the kinetics of polymerization and depolymerizations (1,2).

There are several types of fractionation of polymers. The most generally used type is that involving the various solubilities of the different molecular weight fractions. One solubility method involves fractional precipitation of the various molecular weight fractions. The polymer is dissolved in a solvent and the non-solvent or precipitant is added slowly. The higher molecular weight fractions come out first. The precipitated phase can be separated at intervals from the supernatant liquid, thus giving a fractionation. This process must be carried out very slowly to insure equilibrium. A variation of this method which is sometimes used consists of holding the total solvent composition constant and lowering the temperature of the solution with separation of the precipitated phase at intervals. This method requires very accurate temperature control.

Bronstead was the first to derive an equation relating the solubilities of the various molecular weight fractions (3). He assumed that when dealing with members of a single homologous polymeric series the potential energy is dependent upon the molecular weight and that the distribution between the two phases is a function of the potential energy difference. The large molecules are thus found in the precipitated phase (lower energy level). He derived the following equation in which C' and C" are polymer con-

$$\ln \frac{C'}{C''} = \frac{\lambda M}{RT}$$

centrations of the respective phases in equilibrium and M is the molecular weight of the polymer. λ is an empirical constant independent of M. Schulz later showed that λ does depend somewhat upon M being represented by the following equation where A and B are empirical constants characteristic of the particular polymer (4).

$$\gamma = A + \frac{B}{M}$$

The most recent equations relating solubility and molecular weight take into consideration the entropy of mixing and the activities of the high polymer components. They give the ratio of partial molar volumes of solvent and polymer as a measure of the molecular weight (5,6).

$$\frac{\overline{V_1}}{\overline{V_2}} = V_1 \frac{d}{M}$$

Here V_1 is the molar volume of the pure solvent and $\overline{V_1}$ and $\overline{V_2}$ are the respective partial molar volumes.

Precipitation methods have been generally applied to rubber and other natural hydrocarbons using benzene-alcohol solutions (7,8). Cellulose nitrate, cellulose acetate, cellulose, linear proteins such as gelatin, and starch have been studied by fractional precipitation methods. As an example, cellulose nitrate has been separated into eleven fractions by Spurlin using the precipitation technique (9). The fractions were identified by their absolute viscosities in 5% acetone. These values were uniformly distributed between 2 and 140 centipoises. Other methods of fractionation are more specialized and less used. They include fractional solution, distribution between two immiscible solvents, rate of solution methods, ultracentrifugation, chromatographic adsorption, ultrafiltration, and molecular distillation.

In the fractional solution method, the polymer is extracted with a series of solvent, non-solvent mixtures with increasing solvent content. The low molecular weight fractions were extracted first. The process is repeated until all the polymer has dissolved or until no more will dissolve. A thorough study of these methods as applied to rubber has been made by Bloomfield and Farmer using petroleum ether, ethyl acetate mixtures (10). They separated pale crepe rubber with an average molecular weight of 344,000 into four major fractions as follows: 1.5% of a very low fraction, 60,000; 15% of a low fraction, 216,000; 70% of an intermediate fraction, 324,000; and 12.3% of a high fraction of undetermined molecular weight. The values were determined by intrinsic viscosity methods. Kemp and Peters have carried out similar studies using acetone-hexane mixtures. This method has also been applied to cellulose and its derivatives, gelatin, starch, polyvinyl esters and several of the synthetic rubbers.

It is possible to carry out a fractionation based upon the differential solubility in two immiscible solvents. Bronsted (11) and Schulz and Nordt (12) have shown that the distribution of polymer molecules in such a system depends on the molecular weight. This method is very limited and at present has been used only in a few cases. The diffusion methods are similar to the fractional solution methods but in this case equilibrium conditions are not sought. The method involves placing the polymer in contact with a

solvent, removing the supernatant solution after a definite time interval, replacing it with fresh solvent, and repeating the procedure until the desired number of fractions are obtained. This method has been applied to rubber, nitrocellulose, polyvinyl acetate, and polystyrene. Ultracentrifuge methods are used chiefly to measure the molecular weight rather than as a preparative method, In this method the concentration gradient is measured after the solution has been centrifuged until equilibrium has been obtained. Most of the ultracentrifuge measurements are on linear high polymers. In chromatographic adsorption methods it has been found that the smaller molecules are preferentially adsorbed. The chromatogra is colorless and there is a gradual transition down the column. It is usually divided into an arbitrary number of parts depending on the number of fractions desired. This method was first applied by Mark in 1936 (13). He successfully fractionated cellulose acetate by this method. It has also been applied to lignin and rubber. Ultrafiltration is based on a sieving action. It has been found possible to separate particles of different sizes by ultrafiltration through carefully graded cellulose membranes. This method is better for short molecules since, because of coiling and internal Brownian motion, long molecules may find it more difficult to pass through the pores. It has been principally used in the fractionation of cellulose and its derivatives. Molecular distillation is used more for the purification of a high polymer by removal of the low molecular weight material. It is not a good method for separations. It has been studied to a limited extent by Mark and Raff (14) and Hickman (15) but has never been extensively used.

In general it may be said that the solution precipitation and fractional extraction methods are the most useful. The other methods discussed are less generally applicable and their use depends more upon the character of the polymer.

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Reported by John H. Johnson
May 21, 1948

REACTIONS OF NON-ENOLIZABLE KETONES IN SUNLIGHT

During the last decade, interest in the photochemical reactions of organic compounds has centered mainly on their mechanism; the number of new photochemical reactions of synthetic value discovered in this period is very limited, in particular reactions carried out in sunlight. Considerable progress has been made in the field of non-enolizable ketones in connection with photochemical reactions in sunlight; some of them are important because they furnish an easy way to substances so far unavailable by dark reactions.

Formation of Pinacols.--When an alcohol solution of diaryl ketones is exposed to sunlight, the former is oxidized to an aldehyde or ketone, the latter reduced to benzopinacol (1).

$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}R \quad + \quad R'CHOHR' \quad \rightarrow \quad \underset{OH}{R_2C}\text{—}\underset{OH}{CR_2} \quad + \quad R'COR' \qquad (I)$$

$R = C_6H_5$, $\underline{p}$-$C_6H_4OCH_3$, $\underline{p}$-C_6H_4Cl $\quad R' = CH_3$

Benzohydrols are converted to benzopinacols in the presence of acetone or ethyl methyl ketone (2).

It has been found that the reverse of reaction I also takes place. Thus, xanthopinacol and fluorenpinacol form xanthone and fluorenone respectively (1).

In the presence of small amount of alcoholate, the reaction proceeds further, resulting in the formation of benzohydrol (3).

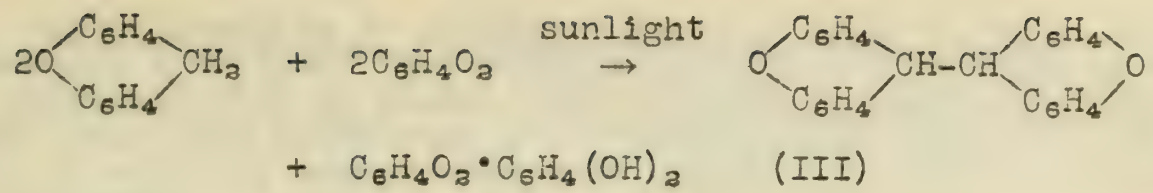
Dehydrogenation Effected by Quinones.--Until recently, only the action of $\underline{p}$-quinones on primary and secondary alcohols has been investigated. Thymoquinone reacts with ethanol, thymohydroquinone and acetaldehyde being formed (4,5).

Benzopinacols are readily dehydrogenated by the action of $\underline{p}$-quinone in sunlight.

$$\underset{OH}{R_2C}\text{—}\underset{CH}{CR_2} \quad + \quad 2C_6H_4O_2 \quad \xrightarrow{\text{sunlight}} \quad 2RCOR \quad + \quad C_6H_4O_2 \cdot C_6H_4(OH)_2 \qquad (II)$$

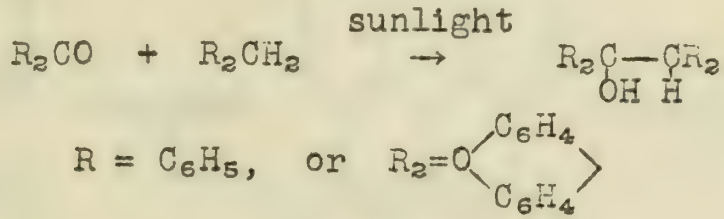
$R = C_6H_5$, $\underline{p}$-$CH_3OC_6H_4$, $\underline{p}$-$CH_3C_6H_4$, $\underline{p}$-ClC_6H_4

The formation of tetraarylethanes from diarylmethanes by the action of quinone in sunlight has been established by Schönberg and Mustafa (1) in the case of diphenylmethane, fluorene, xanthene, anthrone and dinaphthopyran, e.g. xanthene leads to the formation of dixanthyl.



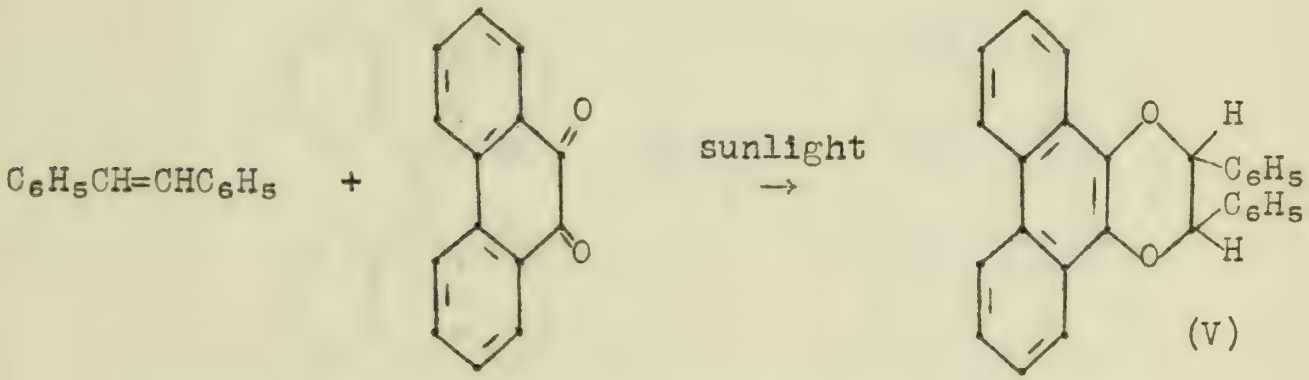
(III)

Addition Reactions.--Diphenyl methane reacts with benzophenone in sunlight with the formation of tetraphenylethyl alcohol.



(IV)

It is interesting to note that when benzil, phenanthrene, quinone, or retenequinone in benzene solution is exposed with olefins in sunlight, addition reaction takes place, leading to the formation of 1,4-dioxins (6,7).

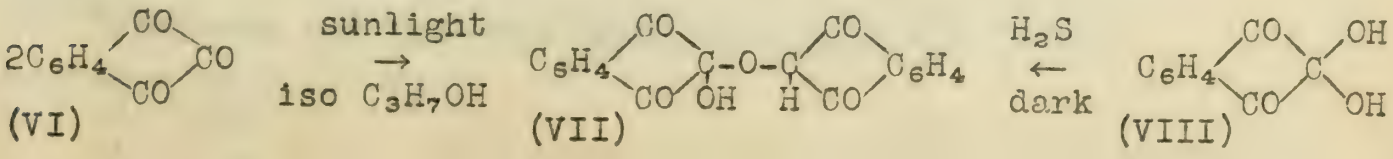


(V)

A number of photoaddition products obtained from 1,2-diketones and ethylenes have been obtained by this method. The value of the reaction lies in the fact that a large number of substances may be synthesized which seem to be inaccessible by any other method so far known.

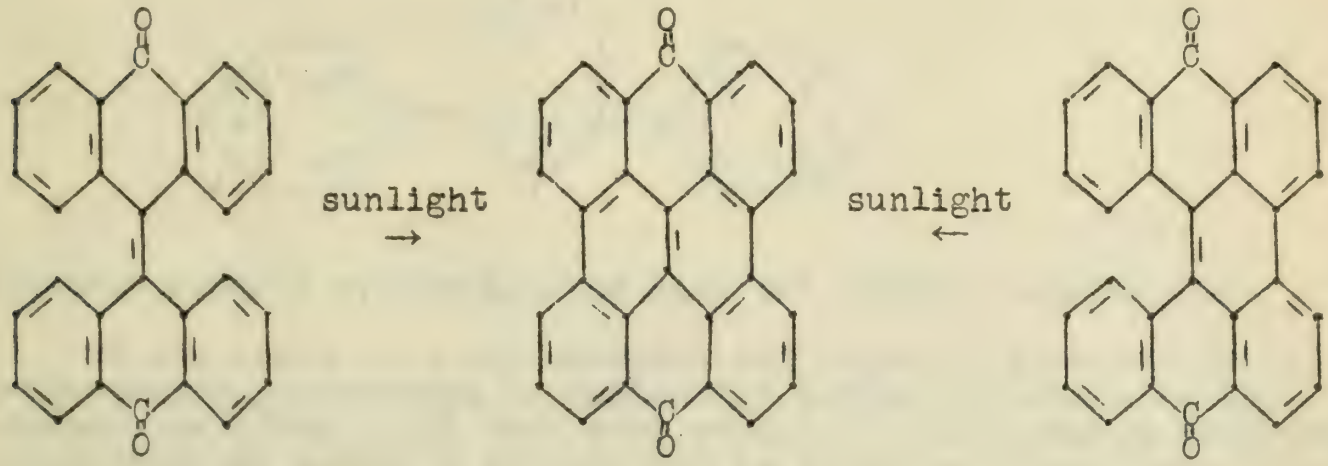
Action of Sunlight of Triketones.--It has been found (9) that when diphenyl triketone in benzene solution is exposed to sunlight, it is converted into benzil. No reaction takes place in the dark.

Triketohydrinene (VI) gives an ether (VII), hydrindantin, which can also be obtained by the action of H_2S on ninhydrin (VIII) in the dark (8).



(VI) (VII) (VIII)

Photoformation of Condensed Aromatic Ring Systems.--Meyer and coworkers (10) found that naphthadianthrone (IX) could be formed by photoformation in acetic acid solution. Schönberg, Ismail and Asker (11) have shown that 10-(9'-xanthylene) anthrone (X) in benzene solution is transformed into oxapenenone (XI) in the presence of sunlight.



(IX)

(X) (XI)

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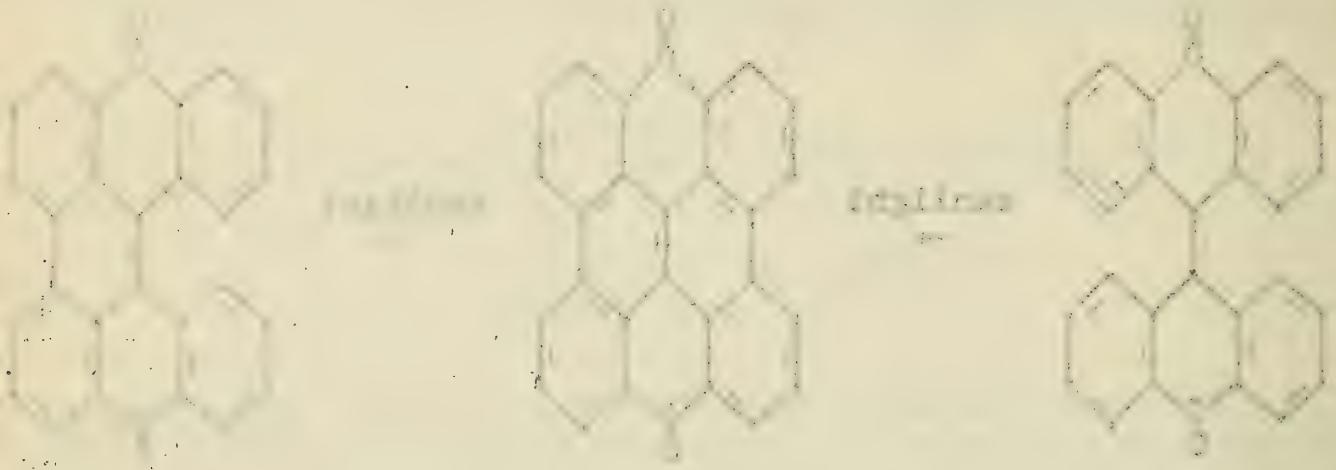
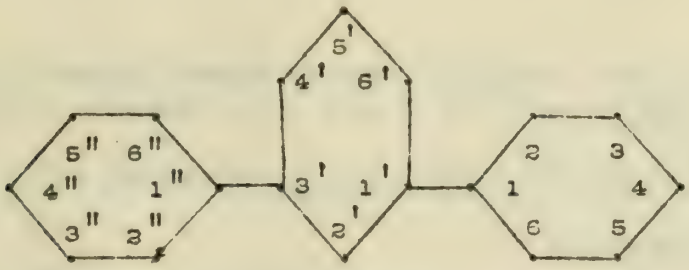


(11)

(12) (13)

THE PREPARATION AND REACTIONS OF THE TERPHENYLS

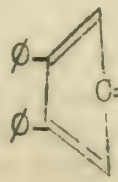
Structure and Numbering.--The current accepted numbering system for the terphenyls is illustrated for the meta isomer.



The same general system is used with the higher "polyphenyls".

On the basis of X-ray analysis and magnetic susceptibility measurements p-terphenyl is assigned a planar structure in the crystalline state (1,2) with some measure of conjugation extending throughout the molecule in solution as evidenced from absorption spectra data (3). No structural study of m-terphenyl itself was found in the literature, but from analogy to sym.-triphenylbenzene (4) in which the substituent phenyl rings are tilted at a 25 degree angle to the central nucleus one might expect m-terphenyl to be non-planar. Absorption data (3) indicate no appreciable conjugation in this molecule. In crystalline o-terphenyl Crews and Lonsdale (5) state that the most probable structure is one in which the two phenyl groups are turned approximately 50 degrees or less out of the plane of the central ring; however, Karle and Brockway (6) concluded from an electron diffraction study that the average position of the two rings is orthogonal to the parent nucleus with possible oscillations of 15 degrees from this normal position.

Preparation.--France, Heilbron and Hey (7), after a systematic study of several preparative methods, concluded that p-terphenyl was best prepared from the reaction of N,N'-dinitrosodiacetyl-1,4-phenylenediamine with benzene, the yield being 55-60%. These same workers synthesized m-terphenyl in a similar manner starting from 3-aminobiphenyl in approximately 22% yield (8). Allen and Pingert (9) decided that the method of Bachmann and Clark (10) - metallic sodium on chlorobenzene - giving yields of 20 to 25% was best for o-terphenyl, even though several by-products are formed. The use of N,N'-dinitrosodiacetyl-1,2-phenylenediamine to prepare the ortho isomer is not reported. Other methods used for preparing the terphenyls include diene syntheses (9,11,12,17)

benzil + acetone $\xrightarrow{\text{KOH}}$  $\xrightarrow[-CO]{\text{M.A.}}$ $\xrightarrow{Ba(OH)_2}$ o-terphenyl (9)

Friedal-Craft Methods (13,14,15,16)

$$\emptyset H + C_6H_{11}Br \xrightarrow{AlCl_3} \emptyset\text{-}C_6H_{11} + \underline{p}\text{-}C_6H_{11}\text{-}C_6H_4\text{-}C_6H_{11} \xrightarrow[160^\circ]{Br_2} \underline{p}\text{-terphenyl} \quad (13)$$

with o-dibromocyclohexane and benzene the m- and p-dicyclohexylbenzenes were formed, no trace of the ortho isomer was found (16).

Organometallic Methods (9,16,18,19,20,21,22)

$$2\text{-biphenylylMgI} + \text{cyclohexanone} \rightarrow \xrightarrow{\text{chloranil}} \underline{o}\text{-terphenyl (20\%)} \quad (9)$$

$$\underline{m}\text{-}C_6H_4Cl_2 + \emptyset Li \rightarrow \underline{m}\text{-terphenyl (17\%)} \quad (22)$$

A novel preparation of 4-amino-p-terphenyl is the reaction between azobenzene and biphenyl in the presence of $AlCl_3$, giving a 40-50% yield of crude material (34).

The individual hydrocarbons are now available from the Monsanto Chemical Company in relatively good states of purity.

Reactions: Nitration.--France, Heilbron and Hey (7) were not able to obtain a mono derivative of p-terphenyl under conditions that suceed with biphenyl but could produce the 4,4"-dinitro and 4,2',4"-trinitro compounds directly from the hydrocarbon; the mono nitro compounds were synthesized indirectly. In the case of m-terphenyl the 4'-nitro, a di-(either the 4,4' or the 4,6' isomer, it is not known which) and a trinitro compound (probably the 4,4', 4" isomer) are obtainable either by stepwise nitration or at once, depending on the reaction conditions (7,8,24). Nitration of o-terphenyl leads to the 4- or the 4,4"- and 2,4- isomers (23).

Halogenation.--Bromine on p-terphenyl in the cold produces the 4-bromo and 4,4"-dibromo compounds, while an excess of the reagent yields a 4,4",x,x-tetrabromo isomer (7). The 2-,3-, and 4-halo derivatives are all formed by the action of 4-nitrosoacetamidobiphenyl on bromo or chlorobenzene. m-Terphenyl and bromine or chlorine give the 4'-halo isomer; excess bromine forms 3,4,4',4"-tetrabromo-m-terphenyl (25,26). Allen and Pingert (9,23) operating under all manner of conditions were unable to monobrominate o-terphenyl, the 4,4"-dibromo isomer always resulting when bromination did occur in these attempts. However, by proper choice of conditions 4,4',4"-tribromo or 4,4',5',4"-tetrabromo-o-terphenyl could be obtained.

Ortho-terphenyl has been found to exhibit some rather unusual properties toward substitution reactions. Traces of water or alcohol, which it retains very tenaciously, promote polybromination and when dissolved in organic solvents, it resists bromination al-

most altogether altough m- and p-terphenyl show no such reluctance. Acetic acid has a very marked effect, for it is possible to boil glacial acetic acid solutions of the hydrocarbon with bromine or fuming nitric acid without appreciable substitution. However, all three terphenyls react in the crystalline state with bromine in the presence of water, the ortho isomer reacting the most readily.

All three hydrocarbons have been perchlorinated (27,28).

Friedal-Craft.--These hydrocarbons undergo the Friedal-Craft reaction leading to either mono or di substitution products at the 4 or 4,4" positions (9,14,18,23,29,30).

Isomerization.--Some care must be exercised when m- and especially o-terphenyl are subjected to Friedal-Craft conditions for it has been found that the latter compound when refluxed in anhydrous benzene in the presence of traces of anhydrous $AlCl_3$ is 94% isomerized to m-terphenyl within fifteen hours, and to a mixture of m- and p-terphenyls within seventy hours, and to p-terphenyl alone at the end of eleven days. Meta-terphenyl was likewise isomerized to the para isomer by traces of the catalyst. With molar amounts of $AlCl_3$ p-terphenyl and triphenylene are formed from o-terphenyl. However, the purified Perrier compound of benzoyl chloride and $AlCl_3$ did not affect either o- or m-terphenyl but gave the normal ketonic product (9).

Miscellaneous.--Schlenk and Bergman (31) obtained a 1',4' disodium adduct of p-terphenyl by the prolonged action of finely divided sodium on an etheral solution of the hydrocarbon; the addition took place more readily in boiling dioxane. Hückel and Datow (32) found that a dihydro compound of p-terphenyl is formed by the action of sodium and liquid ammonia. von Braun and coworkers (19) were not able to chloromethylate p-terphenyl.

Applications and Uses.--Allen and Pingert (33) have been able to make substantive dyes from the 4,4"-diamino derivatives of o- and p-terphenyl by coupling the diazotized amines with suitable agents.

Other uses which have been suggested for these hydrocarbons are as a heat exchange material; when sulfonated, as dye intermediates or as "brighteners" in nickel plating; when halogenated, as a component of casting resin mixtures; as a solid dielectric material in high frequency capacitors; as a wax for citrus fruits and as high temperature lubricants.

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REACTIONS OF ATOMS AND FREE RADICALS IN SOLUTION

I. The Reactions of Diacetyl Peroxide with Aliphatic Ketones. A New Synthesis of 1,4-Diketones.--In 1943 Kharasch reported that the decomposition of diacetyl peroxides in aliphatic acids (1) (both chlorinated and unchlorinated) gave rise to the synthesis of succinic acid and its substitution derivatives. The mechanism presented was as follows:

1. $(CH_3CO)_2O_2 \rightarrow CH_3\cdot + CH_3COO\cdot + CO_2$

2. $CH_3COOH + CH_3\cdot \rightarrow \text{complex} \rightarrow CH_4 + \cdot CH_2COOH$

3. $\cdot CH_2COOH \rightarrow (-CH_2-COOH)_2$

In this scheme, it is assumed that only the methyl free radicals have sufficient energy to remove H atoms from the α-carbon atoms of the acid. The dimerization of the new free radical might be expected since this radical would probably be stabilized by resonance and would require a high energy of activation to react with the solvent.

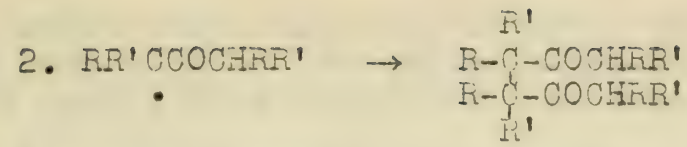
Subsequent studies performed were the removal of hydrogen atoms from esters (2), nitriles (3), acid halides (2), alkyl benzenes and ring-substituted alkylbenzenes (4). In these experiments the following conclusions were made:

1. Carbon dioxide, methane, methyl acetate (or acetyl chloride) are always formed. Little or no methyl chloride is formed.
2. An αH atom is removed from each molecule of acid or acid derivative and two of the univalent radicals then formed dimerize. In the case of the alkylbenzenes, the H atom α to the aromatic ring is removed with subsequent dimerization.
3. Approximately equal quantities of the meso and racemic forms of the dimeric substance are produced.
4. Free radicals with long carbon chains tend to disproportionate, forming saturated and unsaturated hydrocarbons. Thus, dilauryl and dibenzoyl peroxide do not give the products indicated in 1.

The products obtained by the decomposition of diacetyl peroxide on aliphatic ketones can best be explained by assuming that the free methyl radical abstracts an αH atom from the ketone molecule and that the new free radical thus formed dimerizes.

1. $RR'CHCOCHRR' + CH_3\cdot \rightarrow RR'\dot{C}-CO-CHRR'$

(A) (B)



2. RR'CCOCHRR' → R-C(R')-COCHRR' / R-C(R')-COCHRR'

R = alkyl, aryl, or hydrogen atom
R' = alkyl or aryl

(C)

Furthermore, since the dimer (C) contains hydrogen atoms susceptible to attack by free methyl radicals, it is to be expected that trimers and tetramers should occur among the reaction products. In most of the reactions studied, both of these types of reaction products were isolated. In closely related series of compounds, the ease of removal of hydrogen atoms by free methyl radicals follows the order, tertiary > secondary > primary.

The action of free methyl radicals in removing secondary or tertiary rather than primary H atoms is so selective as to give dimers (1,4-diketones) as the major products. No evidence of attack on primary H atoms was found (except with 3,3-dimethylbutanone).

Dimers (1,4-diketones), trimers (triketones), and tetramers (tetraketones) are formed by the action of a diacyl peroxide on ketones whenever the ketones are either aliphatic or of the type aryl-CHR-CO-alkyl (in which R = an H atom or alkyl group); they are not formed from ketones in which an aryl is directly attached to the carbonyl group. Thus only high polymers were formed when acetophenone, propiophenone, or phenyl isopropyl ketone was treated with diacetyl peroxide. Judging by the nature of the gaseous products produced in these reactions, it is probable that some of the methyl free radicals attach themselves to the benzene ring. If this is true, the benzene ring must be greatly activated by the adjacent carbonyl group and competes successfully for free methyl radicals with such active atoms as the secondary and tertiary hydrogen atoms in the alkyl groups of propiophenone and phenyl isopropylketone respectively.

From 50% to quantitative yields of 1,4-diketones are realized.

II. The Addition of Bromo Esters to Olefins.--Investigation of the addition of a number of substances to olefins has demonstrated that some of these additions proceed by a free radical chain reaction. Among the reactions observed are radical induced polymerizations or copolymerizations, and addition of the following types of atoms and free radicals: Br· (5), RS· (6), ·SCH$_2$COOH (7), HO$_3$S· (8), Cl$_3$C·, Br$_3$C· Cl$_2$BrC·, Br$_2$HC· (9), C$_2$H$_5$OCOOCl$_2$· (10), Cl$_2$P· (11), Cl$_3$Si· (12), (C$_6$H$_5$)$_3$C· (13).

The method cited for producing free carboxymethyl radicals or free carbalkoxymethyl radicals cannot be used to study the reactions of these free radicals with olefins because the olefins

successfully compete with the acid or ester for the free methyl radical. The same type of free carbalkoxymethyl radical is, however, produced when a free methyl radical acts on an α-bromo ester.

Since an α-bromine atom in an α-bromo carboxylic ester is more susceptible to attack by a free methyl radical than is an αH atom of an ester or any H atom in an aliphatic olefin, it should be possible by using α-bromo esters to generate free ester radicals in olefinic solvents and to study their reactions with those solvents.

When a small amount of diacetyl peroxide is decomposed in a solution of octene-1 in ethyl bromoacetate a good yield of ethyl-γ-bromocaprate and a small quantity of methyl bromide are obtained. The reaction occurs as follows:

1. $CH_3^{\bullet} + BrCH_2COOC_2H_5 \rightarrow CH_3Br + {}^{\bullet}CH_2COOC_2H_5$

2. $N\text{-}C_6H_{13}CH{=}CH_2 + {}^{\bullet}CH_2COOC_2H_5 \rightarrow N\text{-}C_6H_{13}\underset{\bullet}{C}H\text{-}CH_2CH_2COOC_2H_5$

3. $N\text{-}C_6H_{13}\underset{\bullet}{C}HCH_2CH_2COOC_2H_5 + BrCH_2COOC_2H_5 \rightarrow N\text{-}C_6H_{13}CHBrCH_2CH_2COOC_2H_5$
$+ {}^{\bullet}CH_2COOC_2H_5$

The requisites for such a self-sustaining reaction are: (a) the free carboxylic ester radical and the olefin must be so constituted that they can condense rapidly (step 2); otherwise the concentration of the radical increases to the point where dimerization becomes a successful competitive chain-breaker; (b) the nature of the bromo ester and the new radical produced by the addition of the free carboxylic ester radical to the olefin, must be such as to permit rapid transfer of a bromine atom from the former to the latter.

The following conclusions have been reached regarding the scope of this reaction:

1. This type of condensation reaction yields substituted γ-bromo esters, and these γ-bromo esters have been successfully converted to the corresponding γ-lactones. It has been successfully applied to bromo esters (both straight chain and branched) and to α-bromo dicarboxylic esters, but it fails with β-bromo esters, the reason being that the bromine atom in the β position is but little affected by the carbalkoxy group; this atom is so strongly bound that condition (b) is not fulfilled.
2. Branching of the carbon skeleton of the ester in the vicinity of the position α to the carbalkoxy group slows down the reactivity of the free carboxylic radical with the olefin to the point where accumulation of the free carboxylic radical results in its dimerization. Thus α-bromoisobutyric ester produces considerable quantities of tetramethylsuccinic ester.

3. The bromine atom in ethyl α-bromo-n-butyrate is slightly more reactive toward a secondary free alkyl radical than is the bromine atom in ethyl bromoacetate.
4. The nature of the alcoholic alkyl radical in the ester is not critical, so long as this radical contains no chain-breaking substituent.
5. Straight-chain aliphatic olefins with either terminal or non-terminal double bonds participate successfully in the chain reaction.

As a synthetic method, the free radical addition of an α-bromo ester to an olefin is a simple one-step reaction which lengthens the carbon chain by two carbon atoms and simultaneously introduces a bromine atom in position gamma to the carboxyl group. These bromo compounds are not readily accessible by any other preparative method.

The overall reaction may be formulated as:

$$BrCR_1R_2COOCH_3 + R_3CH{=}CH_2 \rightarrow R_3CHBrCH_2CR_1R_2COOCH_3$$

where the R's are either hydrogen atoms or alkyl groups.

The yield of γ-bromo esters range from 46-77% and the yield of γ-lactones (based on the amount of olefin used) range from 24-64%

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